VOLUME 34 AUGUST 1969 NUMBER 8

Coden: JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED MONTHLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published monthly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

Published monthly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Easton, Pa.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Assistant Senior Production Editor, MARIANNE C. BROGAN; Assistant Editors, FERN S. JACKSON, BARBARA A. RIEGEL.

Advertising Office: Reinhold Publishing Corporation, 600 Summer St., Stamford, Conn. 06904

The American Chemical Society and the Editors of *The Journal of Organic Chemistry* assume no responsibility for the statements and opinions advanced by contributors.

Business and Subscription Information

Correspondence concerning business matters should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Claims for missing numbers will not be allowed (1) if received more than 60 days from date of issue plus time normally required for postal delivery of journal and claim; (2) if loss was due to failure to notify the Subscription Service Department of a change of address; or (3) if the reason for the claim is that a copy is "missing from files."

Change of address: Notify Subscription Service Department, American Chemical Society, 1155 Sixteenth St. N.W., Washington, D. C. 20036. Such notification should include both old and new addresses and postal ZIP number, if any. Please send an old address label, if possible. Allow 4 weeks for change.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should issues of the current volume be out of print at the time the subscription order is received, the pro rata value of such issues will be refunded to the subscriber.

Subscriptions should be renewed promptly, to avoid a break in your series. Orders should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

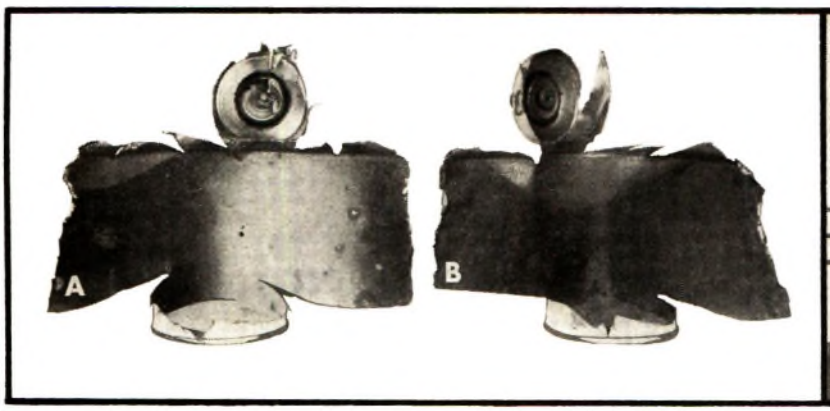
Subscription rates for 1969: $16.00 per volume to members of the ACS and $32.00 per volume to all others. Add $2.50 per subscription for Canada and countries belonging to the Postal Union, and $3.50 for all other countries.

Single copies for current year: $4.00. Postage, single copies: to Canada and countries in the Pan-American Union, $0.15; all other countries, $0.20. Rates for back issues from Volume 20 to date are available from the Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

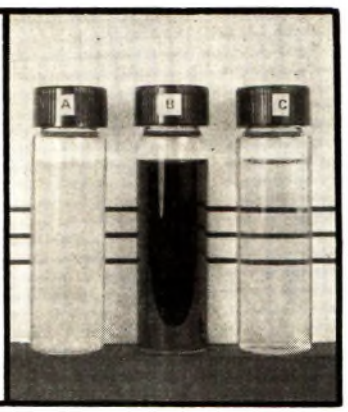
This publication and the other ACS periodical publications are now available on microfim. For information write to: MICROFILM, Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D.C. 20036.

Notice to Authors appears in January, April, July, and October issues

NEW AND INTERESTING FROM PIERCE



Unretouched photograph of the interior of two opened metal cans of currently marketed ninhydrin aerosols showing corrosion and discoloration from interaction of contents and container.



A. Contents of can A showing extreme turbidity. B. Contents of can B showing gross discoloration. C. Contents of Pierce *Nin·Sol* glass package.

NINHYDRIN AEROSOL...*In Shatterproof Glass!*

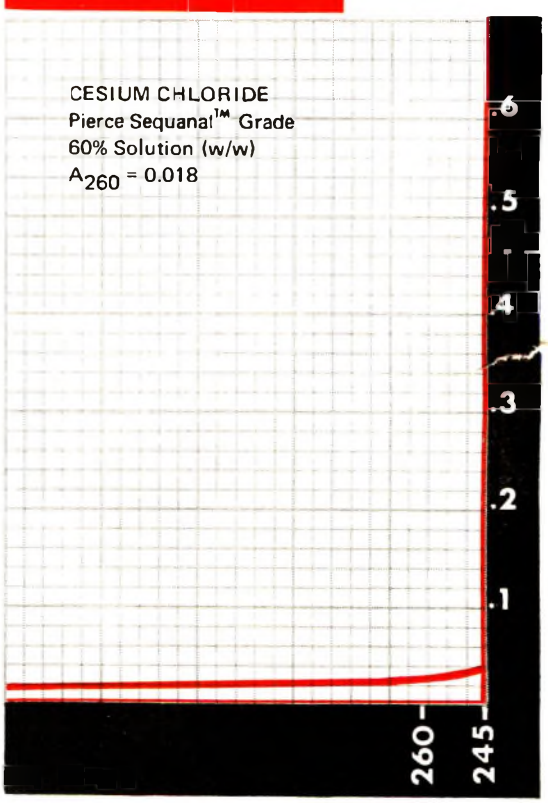
No metal ever touches the reagent in this all glass and plastic system. About 10 years ago we discontinued offering Ninhydrin aerosol because of the high incidence of corrosion and contamination in metal cans. Our new glass bomb with inert plastic valving enables us to offer an immaculate form of this fine reagent. Pierce Reagent Grade Ninhydrin is used exclusively in this product—it is never adulterated or substituted with practical grade. The glass package is shatterproofed with an adequate plastic coating and the bottle size is most convenient for a firm hand hold.

21101 NIN·SOL™ SPRAY, *Ninhydrin Aerosol*
120 ml, 0.25% Ninhydrin, Pierce Reagent Grade in n-Butanol.
$2.50/pkg; 6 pkgs, $2.25/pkg; 12 pkgs, $1.95/pkg

NOW! DENSITY GRADIENT CESIUM CHLORIDE
at Reagent Prices

Nucleic acid and protein chemists will be delighted with Pierce Sequanal™ Grade Cesium Chloride. It is an ultra-pure material showing a maximum absorbance of 0.02 at 260 mμ (60% w/w solution). It's chemical purity is such that there need be no fear of contaminating or degrading specimens. Excellent for either the most exacting analytical purposes or large prep scale work. And very economical for both.

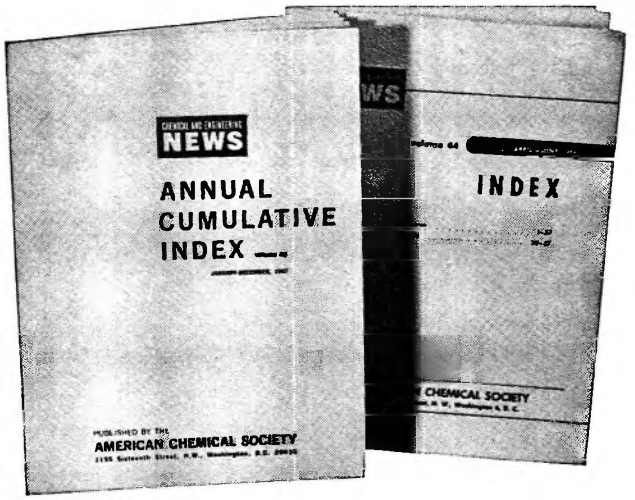
No. 11 1547 Cesium Chloride, Sequanal Grade
$8.50/25g; $25/100g; $200/kg



PIERCE CHEMICAL COMPANY
P. O. Box 117 Rockford, Illinois 61105
PHONE 815/968-0747 TWX 910-631-3419

THE JOURNAL OF Organic Chemistry®

VOLUME 34, NUMBER 8 AUGUST 1969



Chemical and Engineering News
offers an
improved index service

PROMPT QUARTERLY PUBLICATION + ANNUAL CUMULATIVE INDEX

QUARTERLY INDEXES will be mailed about six weeks after the end of each quarter. The schedule will be as follows:

Jan.-Mar.	May 15	July - Sept.	Nov. 15
Apr.-June	Aug. 15	Oct.-Dec.	Feb. 15

SUBJECT INDEXES. All subject indexes are prepared in the Editorial Reference Department of C&EN by technically trained indexers. Specific and general entries are carefully selected to make information retrieval speedy and rewarding. Individual articles are indexed in depth. Product announcements are indexed by subject and company. Books are listed by title and subject.

NAME INDEXES. All individuals mentioned during each quarter are listed, with the single exception of authors of ACS National Meeting Papers. Names of these authors are regularly indexed in ABSTRACTS OF PAPERS and so are not duplicated in the C&EN Name Indexes.

ANNUAL CUMULATIVE INDEX. This combined index will be available shortly after the fourth Quarterly, and will contain all entries from the four quarterlies to provide a single, cumulative index for the year.

USE THIS FORM
TO ENTER YOUR
STANDING ORDER.
MAIL TO:
C&EN INDEXES
1155-16th ST., N.W.,
WASHINGTON, D.C.
20036

Please enter my standing order for the C&EN Index Service checked below, beginning with the 1967 index and continuing until further notice.

_____ **Four Quarterlies + Annual Cumulative.** Price $20.00 Postpaid.

_____ **Annual Cumulative Index Only.** Price $15.00 Postpaid.

SHIP TO

ZIP CODE_____

_____

_____

Invoice same unless otherwise directed. **Signature & Title**

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 34, NUMBER 8

AUGUST 1969

The Bromination of 2-Pyrone

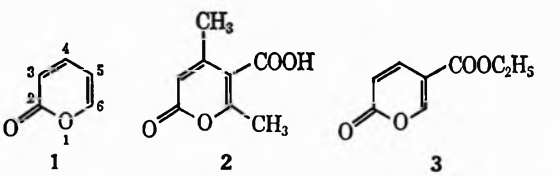
W. H. PIRKLE[1a] AND MARTIN DINES[1b]

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received June 24, 1968

Substituted 2-pyrones are known to undergo substitutive halogenation and other apparently electrophilic substitution reactions. Herein is reported the results of a study of the bromination of unsubstituted 2-pyrone, which has been found to react by an addition–elimination sequence rather than by direct electrophilic substitution. Several intermediate bromine addition products have been isolated and their chemistry has been studied. Several of the addition–elimination products are of particular interest since they are precursors of specifically deuterated 2-pyrones. Chlorination of 2-pyrone also appears to proceed *via* an addition–elimination sequence rather than by direct substitution.

Although the 2-pyrone chromophore, which is common to many naturally occurring physiologically active substances, has been known for quite some time, only recently has the chemistry of the parent compound **1** been the subject of extensive investigation. These investigations include the behavior of 2-pyrone toward light,[2-5] nucleophiles,[6-8] and dienophiles.[9-11] However, no reports of electrophilic substitution reactions upon the parent compound have appeared,[12] although the literature does contain several instances of what seem to be electrophilic substitution reactions upon substituted 2-pyrones. For example, Shusherina, *et al.*, claim to have nitrated,[13] chloromethylated,[14] and chlorosulfonated[15] several 5,6-disubstituted 2-pyrones; however, the proposed structures of the products were not documented as fully as might be desired. Additionally, it seems to be accepted that substituted 2-pyrones can undergo substitutive halogenation. Feist[16,17] found that bromination of isodehydroacetic acid (**2**) or ethyl coumalate (**3**) leads to the 3-substituted bromo derivatives. The Russian workers have employed Feist's studies to assign, by analogy, the structures of the products derived from nitration, chlorosulfonation, and chloromethylation of substituted 2-pyrones. The assumption that these reactions are all mechanistically similar seems implicit in such an approach and is unjustifiable. A sequence involving bromine addition and subsequent elimination of hydrogen bromide could equally well lead to the substitutive bromination observed by Feist, yet need not necessarily give rise to the same products as might aromaticlike electrophilic substitution. This paper reports the results of a study of the halogenation of parent 2-pyrone in which an effort has been made to distinguish between addition–elimination and direct aromaticlike electrophilic substitution pathways.



1 2 3

Results and Discussion

Bromination Studies.—Upon addition of an equimolar amount of bromine to a carbon tetrachloride solution of 2-pyrone, an exothermic reaction ensues and a viscous orange oil separates from solution. Judging from its nmr spectrum,[18] this oil is composed of a complex mixture of brominated pyrones. Overnight

(1) (a) To whom correspondence should be addressed. (b) NSF Summer Fellow, 1965–1966; University of Illinois Fellow, 1965–1966; Archer Daniels Midland Fellow, 1966–1967.

(2) P. de Mayo and R. W. Yip, *Proc. Chem. Soc.*, 84, (1964).

(3) E. J. Corey and J. Streith, *J. Amer. Chem. Soc.*, **86**, 950 (1964).

(4) A. Padwa and R. Hartman, *ibid.*, **88**, 1518 (1966).

(5) P. de Mayo, *Advan. Org. Chem.*, **2**, 394 (1960).

(6) R. Gompper and O. Christmann, *Chem. Ber.*, **94**, 1784, 1795 (1961).

(7) N. Bland and J. F. Thorpe, *J. Chem. Soc.*, **101**, 1557 (1912).

(8) G. Vogel, *J. Org. Chem.*, **30**, 203 (1965).

(9) O. Diels and K. Alder, *Ann.*, **490**, 257 (1931).

(10) H. E. Zimmerman and R. M. Paufler, *J. Amer. Chem. Soc.*, **82**, 1514 (1960).

(11) A. B. Evnin and D. Seyferth, *ibid.*, **89**, 952 (1967).

(12) See, however, W. H. Pirkle and M. Dines, *J. Heterocycl. Chem.*, in press.

(13) N. P. Shusherina, N. D. Dmitrieva, T. F. Kozlova, and R. Y. Levina, *Zh. Obshch. Khim.*, **30**, 2829 (1960).

(14) N. P. Shusherina, N. D. Dmitrieva, and R. Y. Levina, *ibid.*, **31**, 2794 (1961).

(15) N. P. Shusherina, N. D. Dmitrieva, and R. Y. Levina, *Dokl. Akad. Nauk SSSR*, **135**, 1406 (1960).

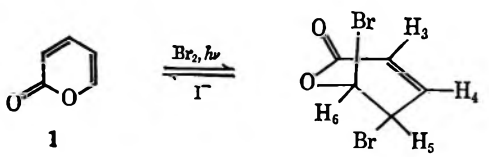
(16) F. Feist, *Ber.*, **26**, 747 (1893).

(17) F. Feist, *ibid.*, **34**, 1996 (1901).

(18) Nmr spectroscopy is most helpful in assigning structures to substituted 2-pyrones since the location of substituents is easily inferred from the magnitudes of the spin–spin coupling constants observed for the remaining ring protons. See W. H. Pirkle and M. Dines, *J. Heterocycl. Chem.*, **6**, 1 (1969).

heating causes this mixture to evolve slowly hydrogen bromide with concomitant disappearance of bromine. Isolable from this reaction is a major crystalline product having the composition $C_5H_3BrO_2$ and exhibiting nmr and infrared spectra in accord with its formulation as 3-bromo-2-pyrone (**4**). This structural assignment is supported by the demonstration that zinc dust–deuterioacetic acid reduction of **8** produces 2-pyrone-3-*d* whose nmr parameters correspond well with those of unlabeled 2-pyrone.[18]

However, this isolable product, 3-bromo-2-pyrone, is not initially present in the complex bromination product mixture. One of the components of this initial mixture can be prepared in high yield and purity by an alternate procedure. At −78°, addition of an equivalent amount of bromine to a solution of 2-pyrone in methylene chloride produces no apparent reaction. However, when the cold solution is irradiated with visible light, rapid photobromination occurs, a 1:1 adduct being the sole reaction product. This adduct, clearly the product of free-radical bromination, is always a major product of the thermal bromination of 2-pyrone even when all reagents are carefully purified, degassed, and the reaction carried out in the dark. Possibly, the adduct arises *via* an ionic mechanism as well as by a radical pathway. Treatment of photodibromide, $C_5H_4Br_2O_2$, with either zinc dust or sodium iodide, results in debromination and 2-pyrone is regenerated. Accordingly, it is clear that the photodibromide has an intact ring and is either the product of 1,2 or 1,4 addition of a molecule of bromine. Analysis of the nmr spectrum[18] of the adduct leads to the assignment of its structure as *dl-trans*-5,6-dibromo-5,6-dihydro-2-pyrone (**5**). The

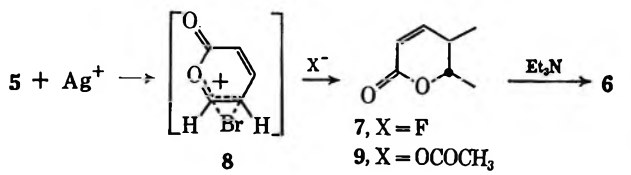


1 **5**

presence of a 9.7-Hz coupling constant points to retention of the C_3–C_4 double bond, and the observation of long-range coupling between H_4 and H_6 is readily explained if **5** has *trans* diaxial bromines, thereby placing H_4, C_4, C_5, C_6, and H_6 in a near planar situation. Such a planar "W" arrangement often leads to observable four-bond coupling.[19] Moreover, a *trans* arrangement of the bromines might be expected to preclude facile *trans* elimination of hydrogen bromide. While **5** is sufficiently stable to allow distillation at *ca.* 100° and 0.2 Torr, it can be dehydrobrominated with triethylamine to produce a new $C_5H_3BrO_2$ isomer, whose nmr spectrum indicates it to be 5-bromo-2-pyrone (**6**), consistent with the observation that zinc dust–deuterioacetic acid reduction of **6** yields 2-pyrone-5-*d*. Further, the production of **6** upon dehydrobromination of **5** lends support to the structure assigned to the photodibromide.

Treatment of photodibromide **5** with silver fluoroborate yields a product, $C_5H_4BrFO_2$, identified as *dl-trans*-5-bromo-6-fluoro-5,6-dihydro-2-pyrone (**7**) from the similarity of its proton nmr spectrum to that of photodibromide **5**, and from its ready conversion into 5-bromo-2-pyrone upon dehydrofluorination with triethylamine. The ^{19}F nmr spectrum of **7** is consistent with this assignment, showing but one resonance (112.8 ppm upfield from internal fluorotrichloromethane) split by coupling constants of 51.0 and 6.0 Hz. These splittings are observed in the proton nmr as well and arise from coupling between fluorine and H_6 and H_5, respectively.

Compound **7** presumably arises from backside attack of fluoride ion upon bridged ion **8**.[20] Silver acetate reacts with photodibromide **5** to afford an analogous product *dl-trans*-5-bromo-6-acetoxy-5,6-dihydro-2-pyrone (**9**) in which acetate rather than fluoride ion has



8

replaced the C_6 bromine. Treatment of **9** with triethylamine leads to 5-bromo-2-pyrone. The conversion of both **7** and **9** into 5-bromo-2-pyrone clearly indicates the location of bromine in these compounds.

While photodibromide **5** is sufficiently stable to allow purification and storage (in the cold), it does undergo gradual decomposition to produce, surprisingly, 3-bromo-2-pyrone. It seemed likely that the formation of **5** from 2-pyrone and bromine is a reversible reaction. If so, then a minor bromination reaction leading to 3-bromo-2-pyrone (or a precursor of this compound) could eventually proceed to an appreciable extent, particularly if an irreversible step (such as loss of hydrogen bromide) were included in the sequence. The formation of photodibromide **5** is reversible; heating a cyclohexene solution of purified photodibromide results in the formation of 2-pyrone and 1,2-dibromocyclohexane.[21] The debromination of photodibromide **5** is promoted by both iodide and bromide ions. Acetonitrile solutions 0.1 *M* in **5** and 1.0 *M* in cyclohexene undergo only slow conversion at 50° into 1,2-dibromocyclohexane and 2-pyrone unless a small quantity of tetra-*n*-butylammonium bromide or sodium iodide is added. These salts profoundly accelerate the debromination of photodibromide **5** and the formation of 1,2-dibromocyclohexane.

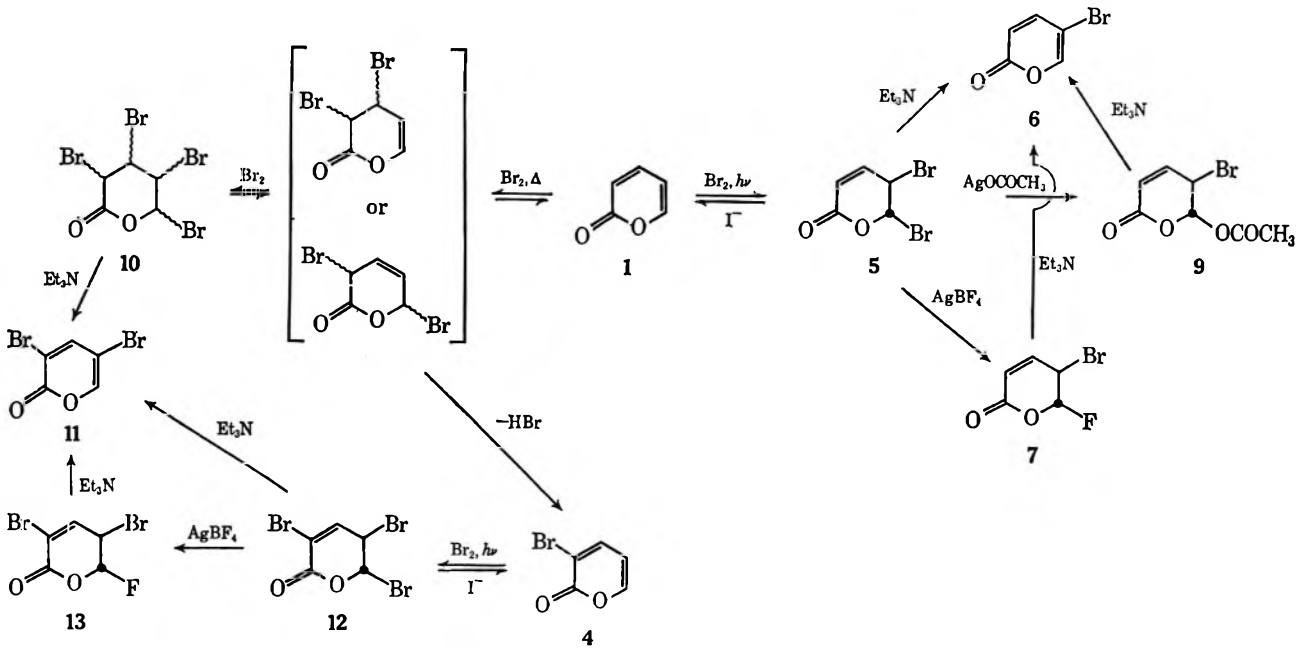
Significantly, purified photodibromide **5** undergoes neither thermal nor photochemical bromination unless hydrogen bromide is added to the reaction mixture. Under these conditions, an additional molar equivalent of bromine is consumed and *dl*-3,4,5,6-tetrabromo-3,4,5,6-tetrahydro-2-pyrone (**10**) is produced. Although the nmr spectrum of **10** has not been completely analyzed, the appearance of two multiplets at δ 6.7 and 4.6–5.4 having relative areas of 1:3 is consistent with the

(19) See, for instance, K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

(20) Examples of fluoroborate ion acting as a source of nucleophilic fluoride are rare; see, for instance, P. Beak, R. J. Trancik, J. B. Mooberry, and P. Y. Johnson, *ibid.*, **88**, 4288 (1966).

(21) In order to verify that this reaction results from liberation of bromine from **5** prior to bromination of cyclohexene rather than by bimolecular bromination of cyclohexene by **5**, the following simple kinetic experiment was undertaken. Diglyme solutions, 0.10 *M* in photodibromide and containing 10- and 20-fold molar excesses of cyclohexene, were maintained at 54.98 ± 0.02°; aliquots were periodically withdrawn; and the formation of 1,2-dibromocyclohexane was followed by vpc analysis. The reaction, proceeding slowly under these conditions, followed smooth first-order kinetics over 2.5 half-lives, having identical rate constants of 7.6×10^{-4}/min. This result demonstrates that slow first-order debromination of **5** is followed by rapid bromination of cyclohexene by the liberated bromine.

SCHEME I

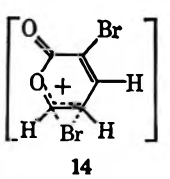


proposed structure. More direct evidence supporting this structural assignment follows from the result of exhaustive dehydrobromination with triethylamine. From this reaction, a crystalline dibromo-2-pyrone may be isolated which is believed to be 3,5-dibromo-2-pyrone (**11**). This structural assignment is based on an nmr spectrum strikingly similar to that of 3,5-dichloro-2-pyrone and further substantiated by the observation that reduction of dibromopyrone **11** with zinc dust in deuterioacetic acid affords 2-pyrone-3,5-d_2.

Even in the absence of added hydrogen bromide, addition of 2.2 molar equiv of bromine to a chloroform solution of 2-pyrone produces **10**. However, since small quantities of hydrogen bromide are evolved from this reaction and since it is known that photodibromide **5** cannot be further brominated except in the presence of hydrogen bromide, one may infer that the tetrabromide **10** arises from initial 1,2 addition of bromine to the 3,4 double bond of 2-pyrone (or by 1,4 addition at C_3 and C_6) followed by the addition of the second mole of bromine. Presumably, a trace of hydrogen bromide arises from dehydrobromination of some dibromide and serves to facilitate the regeneration of 2-pyrone from the rapidly formed photodibromide **5** (which cannot undergo further bromination) and hence ultimately allows complete conversion into tetrabromide **10**.

Although there are several possible stereoisomers of tetrabromide **10**, the *trans,trans,trans* isomer (having all bromine atoms equatorial) is thought to be the major isomer since it should possess the least nonbonded interaction between bromine atoms. Because the all-*trans* equatorial isomer cannot undergo *trans* elimination of hydrogen bromide, it would be expected to be less labile than other stereoisomers of **10**. This compound is relatively stable and can be stored for weeks at 0° with apparently little decomposition. On standing at room temperature or upon warming, the tetrabromide slowly loses hydrogen bromide to form crystalline $C_5H_3Br_3O_2$, formulated as *dl-trans*-3,5,6-tribromo-5,6-dihydro-2-pyrone (**12**) on the basis of the similarity of its nmr parameters to those of photodibromide **5** and its conversion into 3-bromo-2-pyrone by the action of zinc dust or iodide ion, or upon heating with cyclohexene.[22] This tribromide **12** is readily converted into 3,5-dibromo-2-pyrone upon dehydrobromination with triethylamine. Photoaddition of 1 mol of bromine to 3-bromo-2-pyrone also leads to the formation of tribromide **12**.

Addition of an ethylene dichloride solution of silver fluoroborate to tribromo-2-pyrone **12** affords a fluorodibromodihydro-2-pyrone analogous to the formation of fluorobromodihydro-2-pyrone **7** from photodibromide **5** with the same reagent. This compound is assigned the structure *dl-trans*-3,5-dibromo-3,5-dihydro-3-fluoro-2-pyrone (**13**) principally on the basis of its ^{19}F and proton nmr spectra. The fluorine resonance (a doublet of doublets with splittings of 51.0 and 6.0 Hz) falls at 113.1 ppm upfield from internal fluorotrichloromethane. The striking similarity of the nmr spectrum of **13** to those of 5-bromo-6-fluoro-5,6-dihydro-2-pyrone and 3,5,6-tribromo-5,6-dihydro-2-pyrone allows confident structural assignment of **13**. A bridged bromonium ion (**14**) is postulated to be the reaction intermediate.



14

Summarized in Scheme I are the interrelated bromination reactions thus far discussed.

The formation of dihydropyrones **7**, **9**, and **13** from the postulated intermediate bridged ions **8** and **14** deserves further comment. In typical electrophilic aromatic substitutions, the σ complex (an onium ion which may be either a distinct intermediate or a transition state) initially formed may either revert to starting materials or deprotonate to yield the substitution product. To the extent that the action of silver(I) ion

(22) An analogous tribromide has been reported to arise on bromination of 4,6-diphenyl-2-pyrone; see F. Arndt and B. Eistert, *Ber.*, **58**, 2318 (1925).

upon photodibromide **5** or tribromide **12** affords an onium ion intermediate, and to the extent that this onium ion intermediate resembles a σ complex, one may contrast the behavior of 2-pyrone with that of aromatic substances. In the case of the pyrone, the intermediacy of onium ions **7** and **14** seems reasonable; the products obtained are most readily rationalized as arising from the trapping of these ions by nucleophiles. The observed products require that the trapping reactions be much faster than deprotonation or reversible loss of cationic bromine. This behavior is atypical of aromatic systems where σ complexes cannot normally be trapped, but such trapping is not unusual in the reactions of olefins with electrophiles. Thus the failure of 2-pyrone to undergo electrophilic substitution reactions may well be a consequence not of a failure to generate a σ complex, but rather of a failure of the σ complex to deprotonate competitively with nucleophilic attack.

Chlorination of 2-Pyrone.—The chlorination of 2-pyrone, studied less extensively than was bromination, leads one to the conclusion that, in most respects, chlorination sequences parallel those of bromination. The exhaustive photochemically initiated chlorination of 2-pyrone at low temperatures leads to a tetrachlorotetrahydro-2-pyrone **15** whose nmr spectrum is nearly superimposable upon that of the tetrabromotetrahydro-2-pyrone **10**. When the reaction course is followed by nmr spectroscopy, the accumulation of an intermediate whose splitting pattern very closely matches that of photodibromide **5** is observed. Other intermediates are also formed, all eventually yielding the tetrachlorotetrahydro-2-pyrone. This product is readily converted into the known 3,5-dichloro-2-pyrone upon exhaustive dehydrochlorination with triethylamine.

Experimental Section

Reagent grade chemicals were used without further purification unless so specified. All nmr spectra were determined on Varian A-60, A-56/60A, or A-60A spectrometers using *ca.* 15% solutions in deuteriochloroform with tetramethylsilane and fluorotrichloromethane as internal standards. Infrared spectra were run on a Perkin-Elmer 521 spectrophotometer using 10% carbon tetrachloride solutions unless otherwise noted. Ultraviolet spectra were determined on a Perkin-Elmer 202 instrument. Melting points were taken on a Reichert block and are uncorrected, as are boiling points. Indices of refraction were measured on a Carl Zeiss refractometer. Analyses were conducted by Mr. J. Nemeth and his associates of these laboratories; mass spectra were obtained by Mr. J. Wrona using an Atlas CH-4 spectrometer.

2-Pyrone (1).—Coumalic acid was decarboxylated[23] to yield 2-pyrone, bp 110° (15 mm), bp 210–211° (760 mm), n^{25}D 1.5262 [lit.[22] bp 206–209°, n^{25}D 1.5272]. Prior to usage, 2-pyrone was either distilled or chromatographed on silica gel, since it tends to darken and resinify unless stored under nitrogen or below its melting point (*ca.* 0°).

3-Bromo-2-pyrone (4). A. **From the Thermal Decomposition of Photodibromide 5.**—The dark gum which resulted when 0.968 g of photodibromide **5** was allowed to stand at room temperature for 20 days was triturated with methylene chloride and the soluble material was chromatographed on silical gel to yield 0.645 g of 3-bromo-2-pyrone of mp 62°. After sublimation at 50° (0.1 mm), the white crystals had mp 63.5–64°. The carbonyl stretching frequency for the compound occurs at 1748 cm^{-1}, and two sharp peaks are also observed at 1631 and 1535 cm^{-1}. The ultraviolet spectrum of the compound shows $\lambda_{max}^{CCl_4}$ 300 mμ (ϵ 5750). Three equal area quartets can be observed in the compound's nmr spectrum, falling at δ 6.23, 7.56, and 7.77.

(23) H. E. Zimmerman, G. L. Grunewald, and R. N. Paufler, *Org. Syn.*, **46**, 101 (1966).

Anal. Calcd for $C_5H_3BrO_2$: C, 34.40; H, 1.71; mol wt, 174.94. Found: C, 34.21; H, 1.78; mol wt, 175 (mass spectrometric).

B. **From the Direct Action of Bromine on 2-Pyrone.**—To a solution of 12.0 g of bromine in 100 ml of carbon tetrachloride was added 7.5 ml of 2-pyrone (0.09 mol) and the resulting mixture heated to reflux for 14 hr. While hot, the supernatant was decanted from the dark gummy residue and concentrated to half-volume at reduced pressure and cooled, whereupon long needles of 3-bromo-2-pyrone crystallized and were collected. Trituration of the dark gum with hot carbon tetrachloride yielded additional product. After two recrystallizations from carbon tetrachloride, 5.98 g of 3-bromo-2-pyrone of mp 64–65° was obtained. An additional 2.5–3 g of material was isolated from the mother liquors upon fractional sublimation.

C. **From 3,5,6-Tribromo-5,6-dihydro-2-pyrone (12) and Cyclohexene.**—To an nmr tube was added 0.40 ml of a 25% solution of **12** in cyclohexene, and the tube sealed and placed in a steam bath for 30 hr. Examination of the contents by nmr spectroscopy revealed them to be 3-bromo-2-pyrone and 1,2-dibromocyclohexane in a 1:1 mole ratio, plus excess cyclohexene. Subsequent work-up of the products from the nmr tube (fractional sublimation) resulted in the isolation of 25 mg of 3-bromo-2-pyrone, mp 61–63°.

D. **From Treatment of Tribomide 12 with Zinc.**—A solution of 1.40 g of recrystallized tribromide in 40 ml of ethyl ether was treated with *ca.* 2 g of zinc dust at room temperature for 5 hr. The solution was filtered and the residue washed with ether; the combined filtrates were evaporated to dryness at reduced pressure. Upon silica gel chromatography, the residual straw-colored syrup yielded 0.550 g of crystalline product, mp 63–66°, which has an infrared spectrum superimposable with that of an authentic sample of 3-bromo-2-pyrone.

5,6-Dibromo-5,6-dihydro-2-pyrone (5).—In a typical preparation, 5.42 g (0.0565 mol) of freshly distilled 2-pyrone was dissolved in 200 ml of methylene chloride and cooled to −78° in a Dry Ice–isopropyl alcohol bath while a stream of dry nitrogen was bubbled through the solution. Bromine, 9.2 g (0.0575 mol), in *ca.* 20 ml of methylene chloride, was slowly introduced into the cold solution and the mixture irradiated with a 400-W tungsten projector bulb until the bromine had been consumed (3–5 min). After the solvent had been removed (rotary evaporator), the amount of yellow clear oil obtained, 14.6 g, corresponded to quantitative formation of a 1:1 adduct. This adduct was purified by chromatography upon Brinkmann silica gel with methylene chloride and yielded 13.5 g of a clear oil, n^{23}D 1.5933, which, although it can be stored unchanged for several weeks at −20°, evolves hydrogen bromide at room temperature. An imperfect elemental analysis reflects this difficulty. The infrared spectrum shows carbonyl stretching at 1760–70 cm^{-1} and no other bands between 1400 and 1700 cm^{-1}. The ultraviolet spectrum of an ethanolic solution of **5** shows only end absorbtion. In the nmr spectrum of **5**, four equal area multiplets are apparent at δ 5.15 (quartet), 6.20 (doublet), 6.90 (quartet), and 7.20 (octet).

Anal. Calcd for $C_5H_4O_2Br_2$: C, 23.45; H, 1.56; mol wt, 255.92. Found: C, 24.01; H, 1.62; mol wt, 256 (mass spectrometric).

Titration of Active Bromine from Photodibromide 5.—To a solution of 0.212 g (8.3 × 10^{-4} mol) of freshly purified (chromatography on silica gel) photodibromide in *ca.* 5 ml of acetonitrile was added *ca.* 0.5 g of powdered potassium iodide in 5 ml of water. The magnetically stirred slurry was titrated with 15.48 ml of 0.1076 *N* sodium thiosulfate solution to the starch end point. This value corresponds to 1.0 mol of active bromine per mole of photodibromide **5**.

Debromination of Photodibromide 5 with Zinc.—Photodibromide (100 mg) in 1 ml of methylene chloride was treated with *ca.* 0.2 g of zinc dust. After 15 min at 35–40°, the solution was filtered through glass wool into an nmr tube and found, by nmr, to contain only 2-pyrone.

Reaction of Photodibromide 5 with Cyclohexene.—A 25-ml ampoule was sealed after addition of 4.424 g (0.0172 mol) of **5** and 10.0 ml of cyclohexene. After 24 hr in a steam bath, the ampoule was opened. An assay of the products (tlc, nmr) showed that no photodibromide remained. The excess cyclohexene was removed (rotary evaporator), the residue was chromatographed on a column of silica gel with methylene chloride as eluent, and nine 15-ml fractions were taken. Through comparisons with an authentic sample of 1,2-dibromocyclohexane (indices of refraction, boiling

point, infrared spectra, and tlc) fractions 1–3 were shown to be pure 1,2-dibromocyclohexane (3.112 g, 0.0129 mol). Fraction 4 (0.500 g) proved (tlc, infrared spectrum) to be 2-pyrone and 1,2-dibromocyclohexane with the former in preponderance. Fractions 5–9 (1.276 g) were shown by similar methods to be solely 2-pyrone.

Kinetics of the Debromination of 5 in the Presence of Cyclohexene.—Two 10-ml portions of a solution 0.10 *M* in freshly chromatographed photodibromide in diglyme (distilled from sodium) were pipetted into 25-ml volumetric flasks and rubber serum caps affixed. Into these flasks was injected 0.80 ml (0.01 mol) and 1.60 ml (0.20 mol), respectively, of cyclohexene which had been passed through alumina and then distilled. A small quantity (100 mg) of nitrobenzene was added to each flask to serve as an internal vpc standard. Both flasks were immersed in a constant-temperature bath maintained at 54.98 ± 0.02° and aliquots periodically withdrawn and injected into an Aerograph A90-P3 chromatograph using a 5 ft × 0.25 in. column packed with 20% SE-30 on 60/80 Chromosorb W and operating at 130°. The appearance of 1,2-dibromocyclohexane was noted as a function of time. In both cases, identical first-order rate constants of 7.6×10^{-4}/min were obtained.

5-Bromo-2-pyrone (6).—A magnetically stirred solution of 1.010 g of photodibromide **5** in 15 ml of methylene chloride was treated dropwise with a solution of 0.60 ml of triethylamine in methylene chloride (5 ml). After 5 min, the solvent was evaporated and the residue extracted with ether, leaving behind most of the triethylamine hydrobromide. The orange slush (0.794 g) left after evaporation of the ether was chromatographed on silica gel with ether as eluent to yield 0.726 g (91%) of white crystalline 5-bromo-2-pyrone, which, after sublimation at 50° and 0.1 Torr, melted at 60–61°. The carbonyl absorption in the infrared spectrum of this product occurs at 1750–1754 cm^{-1}, with two less intense absorptions at 1613 and 1533 cm^{-1}. The ultraviolet spectrum of **6** shows $\lambda_{max}^{CCl_4}$ 307 mμ (ε 5430). Three equal area quartets were observed in the nmr spectrum of **6**, falling at δ 6.2, 7.3, and 7.5.

Anal. Calcd for $C_5H_3O_2Br$: C, 34.40; H, 1.71; mol wt, 174.94. Found: C, 34.72; H, 1.90; mol wt, 175 (mass spectrometric).

5-Bromo-6-fluoro-5,6-dihydro-2-pyrone (7).—While dry nitrogen was bubbled through a solution of 1.030 g of photodibromide **5** in 50 ml of ethylene dichloride, 4.4 ml of a 1 *M* silver fluoroborate solution in ethylene dichloride was added dropwise with consequent precipitation of silver bromide and evolution of boron trifluoride fumes. After 10 min, the reaction mixture was filtered and the silver bromide washed once with 10 ml of ethylene dichloride. After drying at 110°, the silver bromide weighted 0.644 g (86%). The combined filtrates were dried over anhydrous sodium sulfate and stripped of solvent to leave 0.849 g of colorless oil. This material was chromatographed through a short silica gel column with ether, with consequent isolation of 0.719 g (91%) of **7** as a colorless oil. The product was molecularly distilled prior to elemental and spectral analysis. The infrared spectrum of **7** shows a broad carbonyl absorption centered at *ca.* 1740 cm^{-1} with a low-intensity spike at 1627 cm^{-1}. Only end absorption is observable in its ultraviolet spectrum. The pmr spectrum of **7** contains four equal area multiplets centered at δ 4.7, 6.2, 6.3, and 7.0. The fluorine nmr spectrum consists of a quartet centered at 124 ppm upfield of fluorotrichloromethane.

Anal. Calcd for $C_5H_4BrFO_2$: C, 30.77; H, 2.05; mol wt, 194.95. Found: C, 30.82; H, 1.97; mol wt, 195 (mass spectrometric).

5-Bromo-6-acetoxy-5,6-dihydro-2-pyrone (9).—To a slurry of *ca.* 4 g of silver acetate in 25 ml of methylene chloride, 1.502 g of photodibromide **5** was added, and the resulting heterogeneous reaction mixture magnetically stirred at room temperature for 3 days. The mixture was then filtered and the filtrate passed through a column of silica gel with methylene chloride as eluent. A total of 0.817 g of a yellow solid was eluted which after fractional sublimation gave, as the third sublimation fraction, 0.708 g of white crystalline material melting at 75–77°. A broad band at 1705–1750 cm^{-1} was apparent in the infrared spectrum of the product. Only end absorption is observed in the ultraviolet spectrum of **9** and its nmr spectrum shows four one-proton multiplets at δ 4.70 (quartet), 6.17 (doublet), 6.72 (quartet), and 7.10 (octet), and a three-proton singlet at δ 2.12.

Anal. Calcd for $C_7H_7BrO_4$: C, 35.74; H, 2.97; mol wt, 234.05. Found: C, 35.75; H, 2.93; mol wt, 234 (mass spectrometric).

5-Bromo-2-pyrone (4) from 9.—To a solution of 0.096 g of **9** in 5 ml of methylene chloride, 1 ml of triethylamine was added dropwise, the reaction being worked up in the same manner as was that in which 5-bromo-2-pyrone was prepared from the photodibromide **5**. The product thus obtained (0.057 g) was shown to be identical with the 5-bromo-2-pyrone obtained from **5**.

3,4,5,6-Tetrabromo-3,4,5,6-tetrahydro-2-pyrone (10). A. From the Thermal Bromination of 5.—Dry hydrogen bromide was bubbled into a stirred solution of 1.025 g of photodibromide and 0.25 ml (0.0049 mol) of bromine in methylene chloride (25 ml). After 12 hr, the solvent was evaporated to leave 1.698 g of a reddish oil which was chromatographed with methylene chloride upon a column of silica gel to yield 1.517 g of tetrabromide **10** as a colorless oil. Since it was apparent that at 25° this oil was slowly decomposing with evolution of hydrogen bromide, spectra and elemental analyses were obtained without further purification. This oil shows infrared absorption at 1790 cm^{-1} with no other bands between 1400 and 1800 cm^{-1}. The nmr spectrum of the product consists of two multiplets having area ratios of 3:1. The larger multiplet is complex, centered at about δ 5.0; the smaller appears to be a doublet centered at δ 6.7.

Anal. Calcd for $C_5H_4Br_4O_2$: C, 14.44; H, 0.96. Found: C, 15.14; H, 1.12.

B. From the Thermal Bromination of 2-Pyrone.—Addition of 2 molar equiv of bromine to a hot solution of 1.655 g of 2-pyrone in 25 ml of chloroform causes evolution of small quantities of hydrogen bromide and consumption of the bromine. After 1 hr, the only product isolated from a work-up identical with that outlined in A was 5.648 g (80%) of **10**, as judged by comparison of infrared and nmr spectra.

3,5,6-Tribromo-5,6-dihydro-2-pyrone (12). A. From Tetrabromide 10.—Tetrabromide (5.390 g) in 20 ml of carbon tetrachloride was heated to reflux overnight with consequent evolution of copious amounts of hydrogen bromide. Overnight chilling (0°) of the solution resulted in the deposition of 2.237 g of white crystals of tribromide **12** which were collected and washed with cold carbon tetrachloride. After two sublimations at 100° and 0.01 Torr, the product had mp 92.5–93.0°; it shows bands in its infrared spectrum at 1787, 1772, and 1617 cm^{-1}. The nmr spectrum of **12** is composed of three equal area quartets at δ 5.0, 6.80, and 7.45.

Anal. Calcd for $C_5H_3Br_3O_2$: C, 17.94; H, 0.90; mol wt, 334.83. Found: C, 18.17; H, 1.02; mol wt, 335 (mass spectrometric).

B. From the Photobromination of 3-Bromo-2-pyrone (4).—A solution of 0.743 g of 3-bromo-2-pyrone and 0.680 g of bromine in 200 ml of methylene chloride was irradiated at −78° with a 400-W tungsten projector bulb for 25 min. Upon removal of the solvent, 1.420 g of yellowish crystalline material, mp 87–89°, was obtained. Sublimation under conditions described above raised the melting point to 92–93°. Infrared and nmr spectra of the products of procedures A and B were superimposable.

3,5-Dibromo-2-pyrone (11). A. From 3,5,6-Tribromo-5,6-dihydro-2-pyrone (12).—To a solution of 0.124 g of **12** in 15 ml of methylene chloride was added (dropwise and with stirring) a solution of 1 ml of triethylamine in 5 ml of methylene chloride. After 10 min, the reaction mixture was evaporated to dryness and the solid residue extracted several times with small volumes of methylene chloride. The combined extracts (25 ml) were stripped of solvent and passed through a short silica gel column with ether, eventually yielding 0.087 g of crystalline dibromide **11** which after a single sublimation (50°, 0.1 Torr) melted at 66–67°. The infrared spectrum of a 5% chloroform solution of **11** shows carbonyl absorption at 1755 cm^{-1} and two sharp peaks at 1620 and 1530 cm^{-1}. Ultraviolet absorption, $\lambda_{max}^{CH_2Cl_2}$ 315 mμ (ε 8100), is also noted. The nmr spectrum of **11** shows an AB quartet, the two doublets centered at δ 7.63 and 7.80.

Anal. Calcd for $C_5H_2Br_2O_2$: C, 23.62; H, 0.79; mol wt, 253.90. Found: C, 23.74; H, 0.94; mol wt, 254 (mass spectrometric).

B. From 3,4,5,6-Tetrabromo-3,4,5,6-tetrahydro-2-pyrone (10).—The same procedure as described above was applied to 0.433 g of tetrabromide **10**, and resulted in the isolation of a single product (0.087 g) having mp 64–65° (oil bath) and infrared and nmr spectra identical with those of **11**.

2-Pyrone-3,5-d_2.—To a solution of 2.47 g of 3,5-dibromo-2-pyrone (0.00975 mol) in 15 ml of deuterioacetic acid was added *ca.* 25 g of zinc dust and the nitrogen-blanketed mixture heated on a steam bath for 3 days. The reaction mixture was diluted with 75 ml of warm water and, after the residual zinc was pulverized,

the solution was filtered. The zinc was washed once more with 50 ml of hot water and the extracts were combined. Finally, the zinc was washed with two 75-ml portions of warm methylene chloride and these washings were used to extract the combined aqueous filtrates. The combined methylene chloride extracts were rinsed twice with 50 ml of dilute sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the solvent by evaporation left 0.308 g (33%) of 2-pyrone-3,5-d_2 which was further purified by molecular distillation. The nmr spectrum of the pyrone contains two equal area doublets centered at δ 7.47 and 7.62, both split by 2.4 Hz. Mass spectral analysis showed the product to be 79% doubly deuterated, 20% singly deuterated, and about 1% unlabeled.

3,5-Dibromo-6-fluoro-5,6-dihydro-2-pyrone (13).—Dry nitrogen was bubbled through a solution of 0.927 g of silver fluoroborate in 30 ml of ethylene dichloride while a solution of 1.58 g of 3,5,6-tribromo-5,6-dihydro-2-pyrone (12) in 5 ml of ethylene dichloride was added dropwise. After *ca.* 15 min, evolution of boron trifluoride fumes subsided and the reaction mixture was filtered; the remaining silver bromide was washed with 10 ml of ethylene dichloride. Removal of the solvent from the combined filtrates left 0.946 g of oil which crystallized on standing. After a single recrystallization from carbon tetrachloride, the white crystalline **13** melted at 75–76°. The infrared spectrum (chloroform) of **13** has broad carbonyl absorption at 1745–1775 cm^{-1}. The pmr spectrum is composed of three equal area multiplets centered at δ 4.73, 6.25 (split by 51.0 Hz), and 7.37. The fluorine nmr spectrum shows a quartet centered at 113 ppm upfield of internal fluorotrichloromethane.

Anal. Calcd for $C_5H_3Br_2FO_2$: C, 21.91; H, 1.10. Found: C, 22.21; H, 1.33.

3,4,5,6-Tetrachloro-3,4,5,6-tetrahydro-2-pyrone (15).—While irradiating with a GE 275-W sun lamp, chlorine was slowly bubbled into a solution of 1.979 g of 2-pyrone (0.0207 mol) in 100 ml of methylene chloride which was cooled to −78° in a Dry Ice–acetone bath. After *ca.* 1 hr, the reaction was allowed to warm to −35°, since condensed chlorine was increasing the solution volume. After 1.5 hr at −35°, the solvent and excess chlorine were evaporated to leave *ca.* 5 g of a clear oil ($n^{23}D$ 1.5212) having no noticeable odor of chlorine or hydrogen chloride. The nmr spectrum of the compound is composed of a multiplet at δ 4.4–5.15 (3 H) and a doublet centered at 4.33 (1 H).

Anal. Calcd for $C_5H_4Cl_4O_2$: C, 25.21; H, 1.68. Found: C, 25.20; H, 1.72.

3,5-Dichloro-2-pyrone.—To a solution of 1.776 g of tetrachloride **15** in ether was added dropwise 2 ml of triethylamine in 5 ml of ether. After 5 min, the solution was filtered and the filtrate stripped of solvent, leaving 0.948 g of discolored solid. Chromatography of this product on silica gel resulted in the isolation of 0.735 g of crystalline 3,5-dichloro-2-pyrone melting at 67–70°. After a single sublimation (50°, 0.05 Torr) the melting point was raised to 72.5–73.5° (lit.[24] mp 71–73°).

Registry No.—**1**, 504-31-4; **4**, 19978-32-6; **5**, 19988-79-5; **6**, 19978-33-7; **7**, 19988-77-3; **9**, 19988-78-4; **10**, 19988-73-9; **11**, 19978-41-7; **12**, 19988-74-0; **13**, 19988-75-1; **15**, 19988-76-2.

(24) A. Roedig and G. Markl, *Ann.*, **631**, 1 (1960).

The Synthesis of 9,13b-Dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-6-one

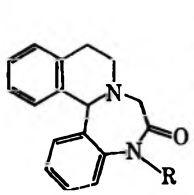
GOETZ E. HARDTMANN AND HANS OTT

Chemistry Research Department, Sandoz Pharmaceuticals, Hanover, New Jersey 07936

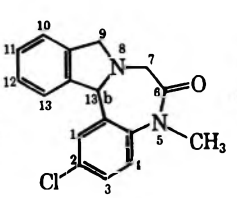
Received October 17, 1968

Two independent syntheses for the new isoindolo[2,1-*d*][1,4]benzodiazepine ring system are described. In one approach 2′-bromomethyl-5-chloro-2-nitrobenzophenone is allowed to react with glycine ethyl ester and the reaction product is reduced with zinc in acetic acid yielding 2-chloro-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]-benzodiazepin-6(7H)-one. The second approach begins with 3-(5-chloro-2-methylaminophenyl)isoindolin-1-one, which on electrolytic reduction followed by alkylation with ethyl bromoacetate and cyclization on heating in acetic acid gives rise to 2-chloro-5-methyl-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]benzodiazepin-6(7H)-one. The syntheses of the respective starting materials are reported. The electrolytic reduction in deuterated solvents is also described.

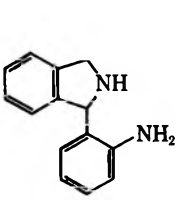
In an earlier publication[1] we reported on the synthesis and the pharmacological activities of tetracyclic benzodiazepines of type **1**. We now[2] wish to report the synthesis of the isoindoline analog **2**, a previously unreported ring system.



1



2



3

In this instance a similar synthetic sequence to that used for the synthesis of **1** would require an N-unsubstituted 1-(*o*-aminophenyl)isoindoline, *e.g.*, **3**, as an intermediate since N alkylation on the isoindoline of this with ethyl bromoacetate and subsequent cyclization would lead to the desired system. Although the synthesis of 1-phenylisoindolines has been described by Veber and Lwowski,[3] we considered **3** not readily available by their reaction sequence. We therefore initially decided to develop a synthesis of **2** not involving the intermediate **3**. This synthesis is outlined in Scheme I.

The structure assigned to **8** is supported by its ir spectrum which showed a strong carbonyl peak at 1740 cm^{-1} and lacked NH or OH absorptions. The nmr spectrum of the crude material was also as expected, showing aromatic and O-ethyl protons as well as an AB quartet for the NCH_2CO protons centered at δ 4.78 (J_{AB} = 16 Hz).

Since larger quantities of **2** were required a second, more economical, sequence was developed as outlined in Scheme II.

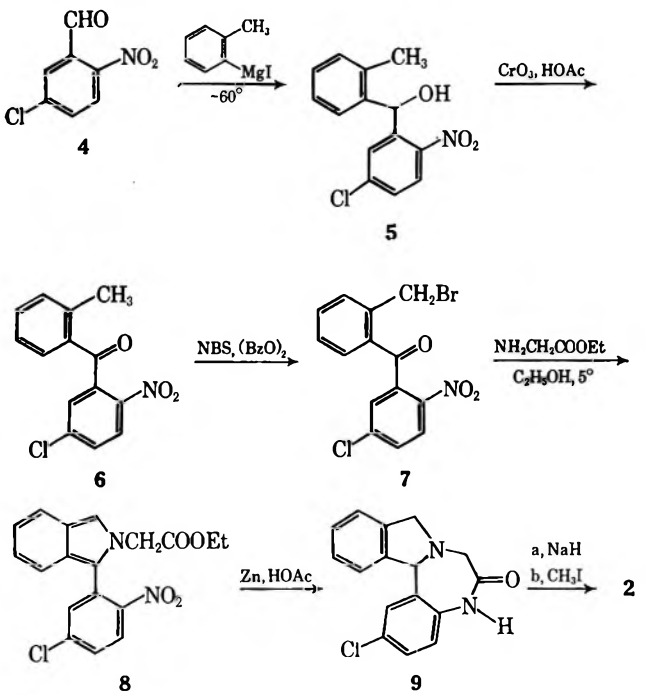
The physical characteristics of the intermediate **13** are in accordance with the structure shown rather than with the corresponding benzophenone imine tautomer (no C=N absorption in ir spectrum). Compound **13**

(1) H. Ott, G. E. Hardtmann, M. Denzer, A. J. Frey, J. H. Gogerty, G. H. Leslie, and J. Trapold, *J. Med. Chem.*, **11**, 777 (1968).

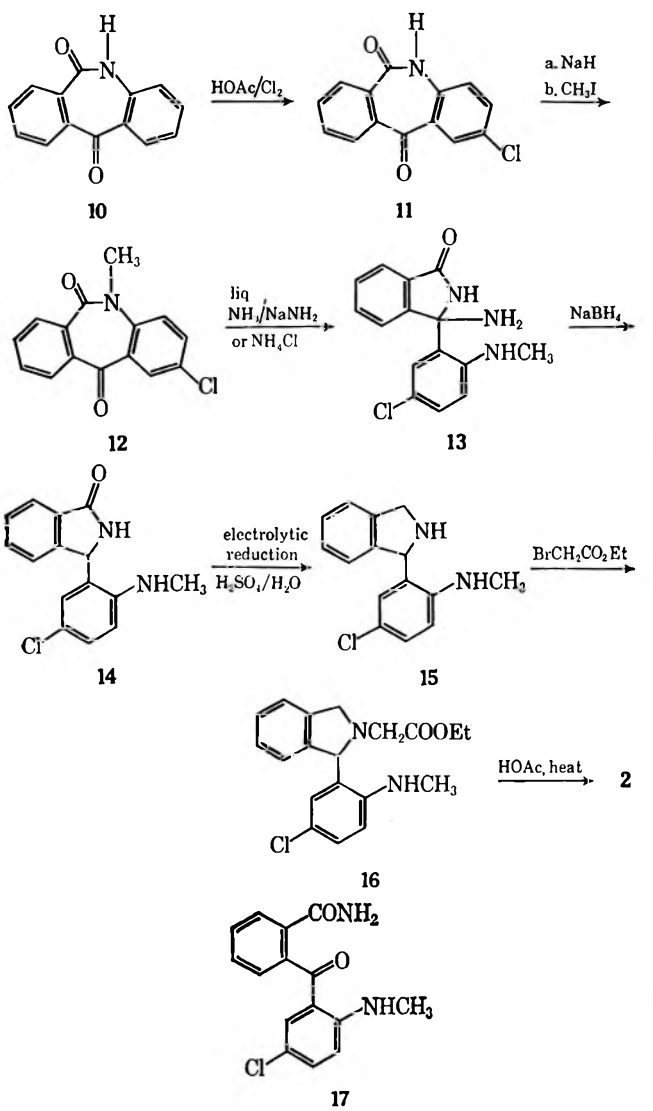
(2) Part of the work described in this paper was published in U. S. Patent 3,375,246 (1968) (to G. E. Hardtmann and H. Ott).

(3) D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.*, **85**, 646 (1963).

SCHEME I



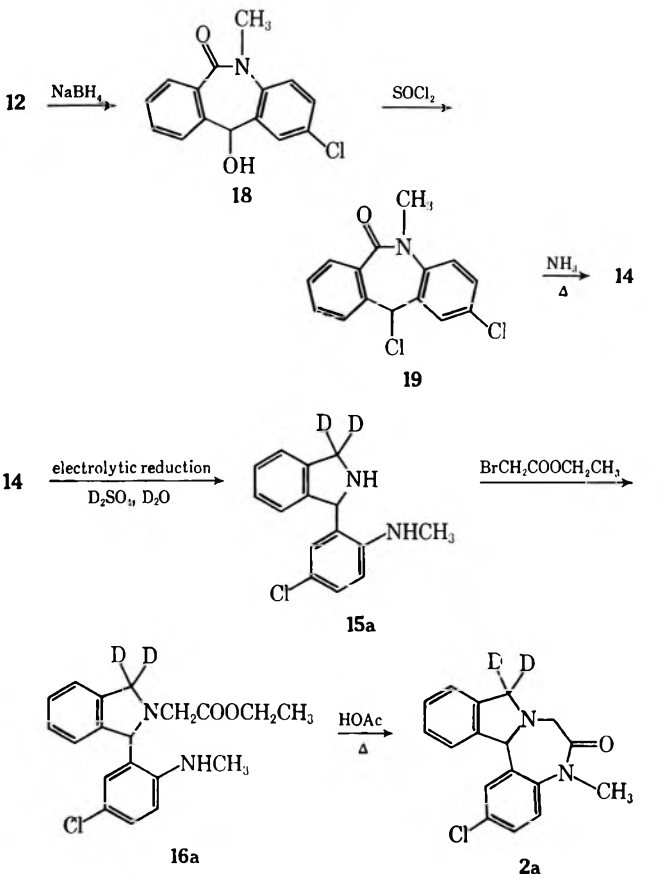
SCHEME II



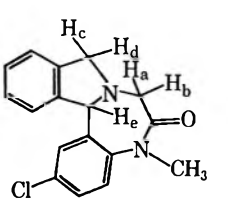
could be reduced to the phthalimidine **14** or could be hydrolyzed to **17**. The phthalimidine **14** was also obtained by the route illustrated in Scheme III. Attempts to reduce **14** with lithium aluminum hydride under various conditions failed. Forcing conditions gave an inseparable mixture while both diisobutylaluminum hydride and diborane reacted only sluggishly with **14**. No isoindoline **15** could be isolated.

It has been reported, however, that phthalimidine can be reduced electrolytically.[4] In this instance, using an apparatus based on that of Coleman and Johnson[5] and aqueous sulfuric acid as the solvent, reduction of **14** was achieved in 50–80% yield. The reduction was also performed in deuterated solvents yielding the dideuterio compound **15a**.

SCHEME III



Compound **2**, prepared by the route shown in Scheme II, was identical in all respects with the material obtained previously. The dideuterated compound **2a** was also prepared.



2

(4) (a) E. W. Cook and W. G. France, *J. Phys. Chem.*, **36**, 2497 (1932); (b) A. Dunet, R. Ratouis, P. Cadiot, and A. Willemart, *Bull. Soc. Chim. Fr.*, 906 (1956).

(5) G. H. Coleman and H. L. Johnson in "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 60.

The nmr spectrum of 2 is worth mentioning. The N-methyl group appears as a broad singlet (half width = 6 Hz) at δ 3.32 which sharpens considerably when the sample is measured either at a higher temperature (45°) or in pyridine.

The protons H_a and H_b are found as a broadened quartet (δ 3.31) and the protons H_c and H_d appear as a multiplet at δ 4.0. This interesting complexity of the H_c,H_d resonance may be due to homoallylic coupling[6] (J = 1.5 Hz) between H_e and either or both of H_c and H_d, and is analogous to that observed in 3,4-dehydroproline derivatives[7] where the long-range coupling can be as high as 6.6 Hz. In our case the coupling assignment is confirmed by either spin–spin decoupling or measuring the dideuterated compound; in both instances H_e is shown as a singlet. No couplings between H_e and H_a or H_b were observed.

Experimental Section

The nmr spectra were obtained on a Varian A-60 spectrometer, the ir spectra (in $CHCl_3$) using a Perkin-Elmer Model 237, and the mass spectra on a LKB 9000. Melting points were determined with a Hoover melting point apparatus and are uncorrected.

Electrodes for the electrolytical reductions consisted of 99.9% lead sheet, 2.5 mm thick. The anode was separated from the rest of the reaction vessel by a Coors 700 porous cup. An automobile battery served as the power source for the electrolysis.

5-Chloro-2′-methyl-2-nitrobenzhydrol (5).—A Grignard solution prepared from magnesium (2.6 g) and *o*-iodotoluene (24 g) in diethyl ether (100 ml) was added at −65° to a solution of 5-chloro-2-nitrobenzaldehyde (15 g) in toluene (250 ml). The mixture was stirred for 3 hr at −60 to −68°, then brought up to −10°, and 20 ml of saturated ammonium chloride solution was added. After the reaction mixture was allowed to warm to room temperature, water and dilute hydrochloric acid were added. The organic phase was separated and the aqueous phase was extracted with ether. The combined extract was dried (Na_2SO_4) and the solvent was evaporated, yielding 12 g of **5** (54%). A sample was recrystallized from ether: mp 129–131°.

Anal. Calcd for $C_{14}H_{12}NO_3Cl$: O, 17.3; Cl, 12.8. Found: O, 17.0; Cl, 12.7.

5-Chloro-2′-methyl-2-nitrobenzophenone (6).—This material was prepared from **5** as described for 2-nitrobenzophenone.[8] From 95 g of **5**, 82 g (90%) of 5-chloro-2′-methyl-2-nitrobenzophenone were obtained. A sample was sublimed at 110° (0.1 mm) and melted at 115–116°.

Anal. Calcd for $C_{14}H_{10}NO_3Cl$: C, 61.0; H, 3.7; N, 5.1; O, 17.4; Cl, 12.9. Found: C, 61.0; H, 3.9; N, 5.1; O, 17.2; Cl, 12.9.

2′-Bromomethyl-5-chloro-2-nitrobenzophenone (7).—The benzophenone **6** (65 g) was dissolved in anhydrous carbon tetrachloride (1500 ml) and a mixture of N-bromo succinimide (45 g) and dibenzoyl peroxide (1.5 g) was added in 5-g portions over a 20-min period. The mixture was heated under reflux for 4 hr, cooled, extracted with water, and evaporated. The crude crystalline product was washed with ethanol and then recrystallized from methylene chloride–ether: mp 137–139°. The yield varied from 45 to 65% depending on the quality of the brominating agent.

Anal. Calcd for $C_{14}H_9BrClNO_3$: Br, 22.5; Cl, 10.0. Found: Br, 22.9; Cl, 9.8.

2-Chloro-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]benzodiazepin-6(7H)-one (9).—A solution of **7** (26.5 g) and glycine ethyl ester (17 g) in a mixture of ethanol (5 l.) and chloroform (400 ml) was stirred at 5° for 30 hr. The solution was concentrated *in vacuo* to about 200 ml after which some starting material, **7** (8 g), could be removed by filtration. The mother liquor was evaporated to dryness *in vacuo*. The residue, dissolved in glacial acetic acid (800 ml), was cooled to 10° and zinc dust (40 g) added in small portions. The mixture was stirred for 3 hr at room temperature and filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in methylene chloride and washed twice with sodium carbonate solution and then with water. After drying (Na_2SO_4) the solution was concentrated and the crystalline product which formed was removed by filtration and recrystallized from ethanol to give **9**, 5.9 g (40%), mp 258–262°.

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.4; H, 4.6; N, 9.8; O, 5.6. Found: C, 67.2; H, 4.8; N, 9.8; O, 5.8.

2-Chloromorphanthridine-6,11(5H)-dione (11).—Morphanthridine-6,11(5H)-dione[9] (100 g) was dissolved in hot glacial acetic acid (2000 ml), a few iodine crystals were added, and a stream of chlorine was introduced into the hot solution (maintained at about 100°). The addition of chlorine was continued until a stiff, porridgelike reaction mixture resulted. After cooling the crystalline product was filtered, washed successively with water, ethanol, and ether, and finally dried under high vacuum. The yields varied between 65 and 85%. Compound **11** melted at 295–298° (lit.[10] mp 293°).

2-Chloro-5-methylmorphanthridine-6,11(5H)-dione (12).—A solution of 2-chloromorphanthridine-6,11(5H)-dione (50 g) in anhydrous dimethylformamide (500 ml) was mixed with a sodium methoxide solution prepared from sodium (5.5 g) and methanol (50 ml). The mixture was evaporated to 125 ml (aspirator) to remove the methanol and warmed to 40°. Methyl iodide (75 ml) was added and the mixture was shaken at room temperature for 1 hr, after which it was poured into water (800 ml) and stirred for an additional hour. The crystals which formed were filtered off, washed with water, and dried to give 35 g (66%) of **12**. After recrystallization from ethanol the product melted at 147–152°. An analytical sample was sublimed at 120° (0.1 mm).

Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.3; H, 3.7; Cl, 13.0; O, 11.8. Found: C, 66.6; H, 3.9; Cl, 13.0; O, 11.5.

3-(5-Chloro-2-methylaminophenyl)isoindolin-1-one (14). Procedure A.—To anhydrous ammonia[11] (150 ml) in a cooled steel vessel, sodium (1 g) was added. After the sodium had all reacted 2-chloro-5-methylmorphanthridine-6,11(5H)-dione (**12**, 22 g) was added and the sealed vessel was heated for 16 hr at 120° (bath temperature). The container was cooled, the ammonia was evaporated, and the crude crystalline product was dissolved in 95% ethanol (400 ml), treated with sodium borohydride (10 g), and heated at reflux temperature for 4 hr. After cooling the excess of sodium borohydride was destroyed with 2 *N* hydrochloric acid (pH 2–3) and the ethanol was evaporated *in vacuo*. The residue was treated with sodium hydroxide (pH 8–9) and extracted several times with ethyl acetate.[12] The crude product was recrystallized from ethanol–chloroform to yield **14** (16 g, 73%): mp 220–226° (recrystallization from chloroform raised the melting point to 229–230°); ir (KBr) 1600, 1610 (C=C), 1700 (amide), 3415, 3200 cm^{-1} (NH).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.1; H, 4.8; Cl, 13.0; N, 10.2; O, 5.9. Found: C, 66.2; H, 5.0; Cl, 13.3; N, 9.9; O, 5.9.

3-Amino-3-(5-chloro-2-methylaminophenyl)isoindolin-1-one (13).—The morphanthridine-6,11-dione **12** (9 g) was added to anhydrous liquid ammonia (80 ml) in small portions. Ammonium chloride (1 g) was introduced and the mixture was heated in a steel cylinder (Parr, No. 4721) at 110° for 16 hr. The cylinder was cooled to room temperature, the ammonia was evaporated, and the residue was dissolved in chloroform (250 ml). The chloroform phase was washed twice with 1% acetic acid, dried (Na_2SO_4), and evaporated *in vacuo*. The remaining brownish product was crystallized from acetone yielding **13** (7.5 g, 80%): mp 183–186°; ir ($CHCl_3$) 1600 (C=C), 1700 (amide), 3295 (NH), 3400 cm^{-1} (broad NH).

Anal. Calcd for $C_{15}H_{14}ClN_3O$: C, 62.6; H, 4.9; N, 14.6; O, 5.6. Found: C, 62.6; H, 5.1; N, 14.6; O, 5.9.

1-(5-Chloro-2-methylaminophenyl)isoindoline (15).—A solution of 3-(5-chloro-2-methylaminophenyl)isoindolin-1-one (**14**, 28.5 g)

(6) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).
(7) W. R. J. Simpson, Ph.D. Thesis, University of Sydney, 1966.
(8) D. H. Hey and R. D. Mulley, *J. Chem. Soc.*, 2276 (1952).
(9) L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arya, *J. Med. Chem.*, **8**, 74 (1965).
(10) (a) A. Wolfram and E. Hausdoerfer, German Patent 551, 256 (1928); *Chem. Abstr.*, **26**, 4344 (1928). (b) A. Drukker and C. I. Judd, *J. Heterocycl. Chem.*, **2**, 276 (1965).
(11) R. W. Chambers and F. H. Carpenter, *J. Amer. Chem. Soc.*, **77**, 1527 (1955).
(12) The product is poorly soluble and on some occasions precipitated in the separatory funnel.

in 65% sulfuric acid (180 ml) was placed into the cathode chamber of the electrolysis apparatus.[10] Water was added (about 150 ml) until the substance just started to precipitate. In the center of the cathode chamber a porous cup (75-mm diameter, Coors porcelain, unglazed) was inserted which was filled with 65% sulfuric acid. The cathode (approximately 180-cm² surface) was inserted into the cathode chamber and the anode of the same size into the porous cup. The mixture was stirred and electrolyzed (6-V automobile battery) with external cooling, keeping the temperature in the cathode chamber between 16 and 22° (to avoid formation of polymers). After 6 hr a fresh battery was connected and the reaction was run an additional 10 hr. The solution in the anode chamber had to be brought back to its original volume by occasional addition of water. While the reaction proceeded samples were removed from time to time and worked up. The reaction was stopped when the carbonyl absorption in the ir spectrum had disappeared. The crude reaction mixture was diluted with twice its volume of ice water, filtered, and neutralized with 50% sodium hydroxide (cooling). The crystalline precipitate which formed was removed by filtration. After drying, the crude product was treated with methylene chloride, the insoluble material was filtered off, and the filtrate was twice extracted with water. The solution was dried (Na_2SO_4), the solvent was evaporated, and the residue was recrystallized from ethanol yielding 19.5 g (72%) of **15**, mp 133–136°.

Anal. Calcd for $C_{15}H_{15}ClN_2$: C, 69.6; H, 5.8; Cl, 13.7; N, 10.8. Found: C, 69.7; H, 6.1; Cl, 13.5; N, 10.8.

2-Chloro-5-methyl-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]-benzodiazepin-6(7H)-one (2). Method A.—A hot solution of **9** (7 g) in dimethylformamide (300 ml) was cooled to 60° and sodium hydride (1.32 g, 56% in mineral oil) was added. After the solution was stirred for 30 min, a clear solution was obtained and then methyl iodide (4 g) in dimethylformamide (50 ml) was added dropwise over a period of 30 min. The mixture was heated at 55° for 1 hr followed by evaporation of the solvent. The residue was dissolved in methylene chloride, extracted with water, and dried (Na_2SO_4) and the solvent was evaporated. The remaining oil was treated with 50 ml of diethyl ether–methylene chloride (1:1), after which the starting material **9** (1.2 g) could be removed by filtration. The filtrate was saturated with anhydrous hydrogen chloride causing crystallization of the hydrochloride of **2**. After recrystallization from ethanol the hydrochloride melted at 263–268° dec.

Anal. Calcd for $C_{17}H_{16}Cl_2N_2O$: C, 60.9; H, 4.8; Cl, 21.2; N, 8.4; O, 4.8. Found: C, 61.0; H, 5.1; Cl, 21.0; N, 8.3; O, 5.1.

The free base **2**, prepared from the hydrochloride by standard procedures, was crystallized from ether and melted [after sublimation at 130° (0.2 mm)] at 169–172°.

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.3; H, 5.1; Cl, 11.9; N, 9.4; O, 5.4. Found: C, 68.3; H, 5.4; Cl, 12.1; N, 9.1; O, 5.5.

Method B.—While a solution of triethylamine (8.4 g) and 1-(5-chloro-2-methylaminophenyl)isoindoline (**15**, 16.9 g) in ethanol (250 ml) was heated at reflux temperature, a solution of ethyl bromoacetate (13.5 g) in ethanol (25 ml) was added (over 10 min). The heating was continued for 2 hr, the solvent was evaporated, and the residue was dissolved in benzene and water. The aqueous phase was extracted with benzene and the combined organic phases were washed with water, dried (Na_2SO_4), and evaporated. A sample of this crude ester (**16**) was crystallized twice from ether to give an analytical sample, mp 78–81°.

Anal. Calcd for $C_{19}H_{21}ClN_2O_2$: C, 66.2; H, 6.1. Found: C, 65.8; H, 6.1.

A solution of the crude product (**16**, 19 g) in glacial acetic acid (150 ml) was slowly concentrated to 50 ml by atmospheric pressure distillation and then evaporated to a solid *in vacuo*. This residue was dissolved in chloroform and, after being washed with sodium hydroxide solution (2 *N*) and with water, the solution was dried (Na_2SO_4) and saturated with hydrogen chloride. Addition of a little ether precipitated the hydrochloride of **2**, which was recrystallized from ethanol (13.5 g), mp 264–269° dec. This material was identical in all respects with that obtained from the methylation of **2**.

2-(2-Methylamino-5-chlorobenzoyl)benzamide (17).—A solution of crude **13** (150 mg) in warm ethanol (8 ml) was treated with dilute hydrochloric acid (2 *N*, 12 ml), giving an instantaneous color change from purple to yellow. After standing for 2 hr at room temperature, the mixture was filtered, and the filtrate was neutralized (2 *N*, NaOH) and extracted twice with chloroform. After being washed with water, the organic phase was evaporated *in vacuo* leaving a residue which was crystallized from methylene chloride–ether. The resulting 52 mg of yellow material melted at 198–201°: uv (CH_3OH) 227.5 mμ (ε 22,000), 399 (4800).

Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.4; H, 4.5; Cl, 12.3; N, 9.7; O, 11.1. Found: C, 62.5; H, 4.6; N, 9.5; O, 10.9.

2-Chloro-11-hydroxy-5-methylmorphanthridin-6(5H)-one (18).—A solution of 2-chloro-5-methylmorphanthridine-6,11(5H)-dione (10 g) in ethanol (150 ml) containing a little chloroform was treated with sodium borohydride and the mixture was stirred at 60° (0.5 hr). The cooled reaction mixture was then acidified with acetic acid, evaporated to half of its original volume, and brought back to pH 8–9 with sodium hydroxide solution. Addition of water (300 ml) precipitated the reaction product **18** (9.4 g, 93%), mp 195–198°.

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.8; H, 4.4; Cl, 12.9. Found: C, 65.9; H, 4.6; Cl, 12.8.

2,11-Dichloro-5-methylmorphanthridin-6(5H)-one (19).—A solution of 2-chloro-11-hydroxy-5-methylmorphanthridin-6-(5H)-one (8.5 g) in thionyl chloride (120 ml) was heated at reflux temperature for 3 hr. After this solution was evaporated to dryness, the residue was dissolved in benzene, and the solution was again evaporated to dryness; the solid remaining was crystallized from methylene chloride–ether to yield 8.8 g (93%) of **19**, mp 188–190°.

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.7; H, 3.8; Cl, 24.3. Found: C, 61.4; H, 4.0; Cl, 24.1.

3-(5-Chloro-2-methylaminophenyl)isoindolin-1-one (14). Procedure B.—2,11-Dichloro-5-methylmorphanthridin-6(5H)-one (0.5 g) was heated with liquid ammonia (approximately 10 ml) in a sealed steel vessel at 100° (bath temperature) for 16 hr.[13] After cooling, the ammonia was allowed to evaporate, and the crystalline residue was washed with water, dried, and crystallized from ethanol–acetone (1:1) to give **14** (0.19 g), mp 227–229°, identical with the product obtained by the alternative route above.

1-(5-Chloro-2-methylaminophenyl)isoindoline-3,3-$^2H_2$ (15a).—For this electrolytic reduction an apparatus similar to, but smaller than, that described for the preparation of **15**, was used. The electrodes each had a surface area of 50 cm², and an automobile battery (6 V) was again used as the energy source. The reaction was followed by the periodic working up of samples, the ir spectra of which were checked for the disappearance of carbonyl absorption. A solution of 3-(5-chloro-2-methylaminophenyl)isoindolin-1-one (3.5 g) in a mixture of concentrated dideuteriosulfuric acid (45 ml) and deuterium oxide (45 ml) was diluted with an additional 40 ml of deuterium oxide and electrolyzed at 15–25° until the ir spectrum lacked carbonyl absorption. The reaction mixture was then neutralized with 50% NaOH solution (with cooling) and extracted twice with chloroform. Evaporation of the dried extract followed by recrystallization from ether gave **15a** (2.6 g): mp 134–136°; mass spectrum (70 eV) *m/e* 260 (M^+).

1-(5-Chloro-2-methylaminophenyl)isoindoline-3,3-$^2H_2$-2-acetic Acid Ethyl Ester (16a).—A solution of **15a** (1.8 g) in ethanol (50 ml) containing ethyl bromoacetate (1.8 g) and triethylamine (1.2 g) was heated at reflux temperature for 4 hr. The reaction mixture was evaporated to dryness and the residue was dissolved in ether–benzene (1:1) and a little water. The mixture was then extracted with water and saturated sodium chloride solution, dried, and evaporated *in vacuo*. The residue obtained was dissolved in pentane–ether (9:1) and filtered through silica gel. On partial evaporation of the solvent compound **16a** (2.2 g) crystallized out. A portion was recrystallized from ether–pentane: mp 80–83°.

Anal. Calcd for $C_{19}H_{19}N_2O_2Cl^2H_2$: C, 65.8; H, 6.7; N, 8.1. Found: C, 65.8; H, 6.4; N, 8.1.

2-Chloro-5-methyl-9,13b-dihydro-5H-isoindolo[2,1][1,4]benzodiazepin-9,9-$^2H_2$-6(7H)-one (2a).—A solution of **16a** (0.9 g) in acetic acid (40 ml) was heated at reflux temperature for 4 hr, during which time 6 ml of the solvent were slowly distilled off. The reaction mixture was then evaporated *in vacuo* and a solution of the residue in benzene was washed with water and saturated sodium chloride solution. Evaporation of the solvent left an oil (0.67 g) which was crystallized from ether to give **2a** (0.44 g): mp 171–174°; mass spectrum (70 eV) *m/e* 300 (M^+).

Anal. Calcd for $C_{17}H_{13}N_2OCl^2H_2$: C, 67.9; H, 5.7; Cl, 11.8. Found: C, 67.4; H, 5.7; Cl, 11.8.

(13) A similar reaction was described by F. Hunziker, F. Künzle, and J. Schmutz [*Helv. Chim. Acta*, **49**, 1434 (1966)], who obtained a substituted phthalide from an 11-hydroxymorphanthridine.

Registry No.—2, 19991-27-6; 2 hydrochloride, 16175-40-9; 2a, 20013-27-8; 5, 19991-29-8; 6, 16219-20-8; 7, 16175-45-4; 9, 16175-46-5; 12, 16219-18-4; 13, 16175-31-8; 14, 16175-32-9; 15, 19980-11-1; 15a, 19980-12-2; 16, 16175-38-5; 16a, 19980-15-5; 17, 19980-16-6; 18, 16175-33-0; 19, 16219-19-5.

Acknowledgments.—We wish to thank Mr. G. Bamert for assistance in the experimental work. We are very grateful to Mr. Urs Stoeckli and Mrs. N. Engstrom and their staff for the spectral and microanalytical work as well as for aid in the interpretation of the spectral data.

The Addition of Acetone Dimethylhydrazone to Dimethyl Acetylenedicarboxylate

STEPHEN F. NELSEN

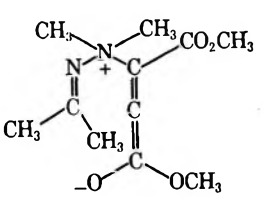
Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received November 8, 1968

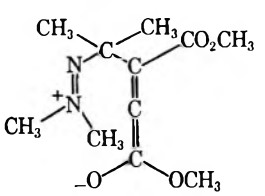
Acetone N,N-dimethylhydrazone and dimethyl acetylenedicarboxylate react at −30° to give 20% of the 1:2 adduct, 1-dimethylamino-2,2-dimethyl-3,4,5,6-tetracarbomethoxy-1,2-dihydropyridine, and 26% of a 1:1 adduct, dimethyl N-isopropylidine-N-dimethylamino-2-aminomaleate. At higher temperatures dimethyl 2-dimethylaminomaleate becomes an increasingly more important product. Dimethyloxalacetate dimethylhydrazone is a minor product at low temperatures. The 1:2 adduct gave upon photolysis the *cis* and *trans* forms of the azahexatriene, the former closing thermally at room temperature.

Hydrazones have three potentially nucleophilic centers: the amino nitrogen, the imino nitrogen, and the imino carbon. Alkylation of dimethylhydrazones takes place exclusively at the amino nitrogen,[1] which clearly ought to be the most nucleophilic center.

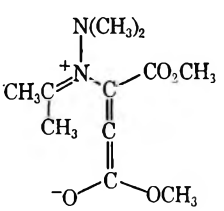
Dehydrodimerization of formaldehyde phenylhydrazone to glyoxal osazone, reported by von Pechmann,[2] presumably involves a nucleophilic attack at the carbon in the carbon–carbon bond-forming step. We felt that addition of dimethylhydrazones to dimethyl acetylenedicarboxylate[3] (1) would be an example of a nucleophilic reaction of a hydrazone which might give reaction at any of all of the nucleophilic centers. Since the initial addition to form zwitterions should be reversible, the products obtained would reflect the ease of subsequent reactions to give stable products. Dimethylamino nitrogen attack by acetone dimethylhydrazone (2) would yield zwitterion **3**, which



3



4

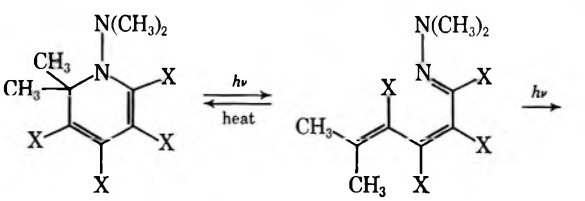


5

would be expected to undergo N–N$^+$ bond fission and give 2-dimethylamino dimethylmaleate. Attack by the imino carbon would give **4**, which by analogy with enamine adducts[3] might be expected to close to the azacyclobutene structure, which would open to the azabutadiene form easily. Imino nitrogen attack would give **5**, which would be expected to react as adducts of pyridines[3] and other imines,[4] and either add another molecule of dimethyl acetylenedicarboxylate in a "1,4-dipolar" reaction[4a] or transfer a C-methyl hydrogen.

Results and Discussion

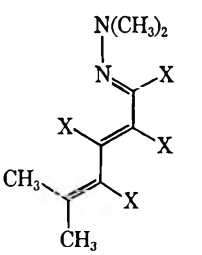
When **1** and **2** are mixed in methylene chloride at −30°, the reaction is complete in several hours. To consume all of the hydrazone, a molar ratio of 1.5:1 is required. Removal of solvent affords a yellow solid having spectral and analytical data consistent with **6**, an expected product of initial imino nitrogen attack. The behavior of **6** upon ultraviolet irradiation confirms this structural assignment, for it is partially converted into



6

X = CO_2CH_3

7



8

an isomer, **7**. The nmr spectrum of **7** shows the downfield shifted dimethylamino absorption and nonequivalent allylic methyls expected for simple ring opening of the azahexadiene ring of **6**. At room temperature in carbon tetrachloride **7** reverts to **6** with a

(1) (a) R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27**, 4372 (1962); (b) P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).

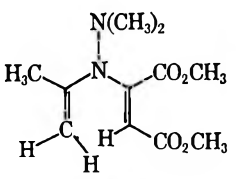
(2) H. von Pechmann, *Chem. Ber.*, **30**, 2459 (1897).

(3) For a recent review of such addition reactions, see E. Winterfeldt, *Angew. Chem. Intern. Ed. Engl.*, **6**, 423 (1967).

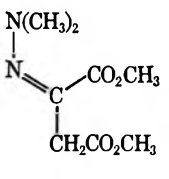
(4) (a) R. Huisgen and K. Herbig, *Ann. Chem.*, **688**, 98 (1965); (b) J. M. F. Gagan, *J. Chem. Soc., C*, 1966, 1121.

half-life of about 55 hr (analysis by nmr). Prolonged irradiation of **6** causes other products to be formed, of which the only one investigated was **8**, also an isomer. The nmr of **8** is quite similar to **7** but slightly shifted, and heating a mixture of **6**, **7**, and **8** with boiling acetone for 3 hr cyclized the **7** to **6** without affecting **8**. Thus **7** is the *cis* isomer, and **8** the *trans* isomer of the ring-opened material.

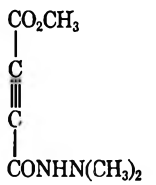
Only about 30% of the residue from the reaction of acetone dimethylhydrazone with dimethyl acetylenedicarboxylate after crystallization of **6** was distillable, and decomposition was apparent. The resinous pot residue was not investigated. The distillate consisted of two major components, **9** and **10**, which we could not separate analytically. Spectral data for **9** showed it to be dimethyl N-isopropylidine-N-dimethylamino-2-aminomaleate. That **9** has the maleic ester geometry is demonstrated by comparison of its nmr spectrum with those of the piperidine adducts of 1[5] which have vinyl hydrogen absorption at δ 4.83 for the maleic, and 5.48 for the fumaric form (compared with 4.61 for **9**). The methoxyl separation substantiates the argument, for it is 0.22 ppm in the maleic and 0.00 ppm in the fumaric piperidine adduct, compared with 0.21 ppm for **9**. Thus **9** is the other expected product from **5**, the zwitterion formed by imino nitrogen attack.



9



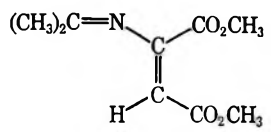
10



11

The lower boiling component of the mixture had spectral data consistent with it being the N,N-dimethylhydrazone of oxalacetic acid (**10**). The corresponding phenylmethylhydrazone has been prepared by addition of 1-phenyl-1-methylhydrazine to dimethyl acetylenedicarboxylate.[6] The major product from addition of dimethylhydrazine to dimethyl acetylenedicarboxylate was, indeed, **10**. When this reaction is run at $-30°$, however, the major product is the solid monodimethylhydrazide (**11**), which was not detected in our reaction mixtures; so it is unlikely that **10** was formed by contamination of the acetone dimethylhydrazone with dimethylhydrazine. Adventitious hydrolysis of **9** is an obvious possibility.

When the reaction of acetone dimethylhydrazone with dimethyl acetylenedicarboxylate is run at higher temperatures, **10** becomes a much less important product, and dimethyl 2-dimethylaminomaleate[5] (**12**) appears in isolable amounts. Yields calculated from the nmr spectra of the distillate and isolated weight of **6** are summarized in Table I. The bisenamine **9** is quite unstable to heating, vpc, or tlc, giving a variety of products, mostly intractable. The major nonvolatile products which come off an SE-30 vpc column upon injection of **9** are **10** and **13**. The spectral properties of **13** show it to be the acetone imine of dimethyl 2-aminomaleate. The downfield nmr shift for the vinyl hydrogen in comparison with **9** is expected since the imino nitrogen of **13** should be less capable of releasing



13

electrons to the maleic ester system. A similar effect is reported by Truce and Brady,[7] who compare vinyl shifts for dialkylamino and ethylenimine adducts with **1**, although in this case nitrogen hybridization is changed by inclusion in a three-membered ring. The vinylic methyls remain a singlet in benzene, making it unlikely that an accidental shift correspondence is responsible; inversion at the imino nitrogen appears to be rapid. **13** would also have been a possible product from internal proton transfer by **5**, splitting out formaldehyde methylimine; no **13** was detected in the reactions of **1** with **2**, however.

The reaction of **1** with formaldehyde dimethylhydrazone was looked at briefly, but even at $-50°$ no 1:1 or 2:1 products were observed. At higher temperatures small amounts of **12** were formed, as was the case with acetone dimethylhydrazone.

In conclusion, acetone dimethylhydrazone (**2**) reacts with **1** as an imine (through **5**), and no evidence for "azaenamine" reaction (proceeding through nucleophilic attack by carbon to give zwitterion **4**) was found. Above 0°, the product from N–N$^+$ fission of zwitterion **3** becomes increasingly important.

TABLE I

PRODUCTS (PER CENT) OF THE REACTION OF 1 AND 2 IN METHYLENE CHLORIDE (1:1 MOLAR RATIO)

	Temp, °C		
Product	−30	0	40
6	16[a]	8	4
9	26	17	25
10	7	1	1
12	1	4	7

[a] Using a 1.26:1 ratio of 2:1, 22% was isolated.

Experimental Section

Melting points were taken on a Fisher-Johns capillary apparatus, and are uncorrected. Nmr spectra were run on a Varian A-60A, and are reported as parts per million shift downfield from internal TMS. Ir spectra were taken using carbon tetrachloride on a Beckman IR-8, uv using a Cary 11, and mass spectra using a CEC 103 or AEI MS 9. Combustion analyses were by Microtech. Dimethyl acetylenedicarboxylate was distilled commercial material (Aldrich), and contained about 0.6% dimethylfumarate. Acetone N,N-dimethylhydrazone (bp 93–95°, lit.[8] bp 92–94°) was prepared by mixing equimolar quantities of acetone and N,N-dimethylhydrazine (untreated Aldrich), stirring for 4 hr, adding sodium hydroxide pellets until an aqueous layer stopped forming, and distilling from sodium hydroxide.

1-Dimethylamino-2,2-dimethyl-3,4,5,6-tetracarbomethoxy-1,2-dihydropyridine (6).—Acetone dimethylhydrazone (5.0 g, 0.05 mol) in 10 ml of methylene chloride was cooled to $-30°$, poured into a cooled solution of 9.0 g (0.063 mol) of **1** in 10 ml of methylene chloride, and stored 15 hr at $-30°$. Solvent was removed at aspirator pressure; the residue was stirred with 20 ml of carbon tetrachloride and filtered, washing well with carbon tetrachloride. The brown solid was crystallized once from chloroform–heptane

(5) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

(6) R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1148 (1962).

(7) W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).

(8) R. H. Wiley, S. C. Slaymaker, and H. Kraus, *ibid.*, **22**, 204 (1957).

to give 4.3 g (22%) of **6**, mp 141–143°. Two recrystallizations from $CHCl_3$ gave mp 142–143°; nmr ($CDCl_3$) δ 1.61 (s, 6, $C(CH_3)_2$), 2.87 (s, 6, $N(CH_3)_2$), 3.62 (s, 3, OCH_3), 3.68 (s, 3, OCH_3), 3.74 (s, 3, OCH_3), 3.84 (s, 3, OCH_3); ir (CCl_4) 5.76–5.90, 6.23, 6.51, 6.79 μ; uv max (MeOH) 271 nm (ϵ 1.10×10^4), 354 (5.8×10^3).

Anal. Calcd for $C_{13}H_{24}N_2O_8$: C, 53.12; H, 6.29; N, 7.29. Found: C, 52.93; H, 6.26; N, 7.26.

Irradiation of 6.—A solution of 0.5 g of **6** in 350 ml of dry ether under N_2 was irradiated with a 450-W Hanovia "L" lamp, using a Pyrex well, for 50 min. Solvent was removed at aspirator pressure, and nmr indicated a 40% conversion into **7**. Recrystallization from CCl_4 gave **7**: mp 110-112° (resolidified and remelted 141–143°); nmr ($CDCl_3$) 1.79 (s, 3, $-CCH_3$), 2.07 (s, 3, $=CCH_3$), 3.06 (s, 6, $N(C_3)H_2$), 3.61 (s, 3, OCH_3), 3.66 (s, 3, OCH_3), 3.72 (s, 3, OCH_3); uv (MeOH) 282 nm (ϵ 7.8×10^3), 349 (3.2×10^3). In deuteriochloroform, the half-life for cyclization of **7** to **6** is about 55 hr at room temperature.

Irradiation of **6** for 24 hr gave other materials; the only one investigated (**8**) had an nmr spectrum very similar to that of **7**, though shifted—(CCl_4) δ 1.90 (s, 3, $=CCH_3$), 2.24 (s, 3, $=CCH_3$) 3.01 (s, 6, $N(CH_3)_2$), 3.60 (s, 3, OCH_3), 3.66 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 3.78 (s, 3, OCH_3). Heating a mixture of **6**, **7**, and **8** in chloroform with refluxing acetone for 3 hr converted the **7** into **6** without affecting the **8**. We never obtained **8** in crystalline form.

Dimethyl N-Isopropylidine-N-dimethylamino-2-aminomaleate (9).—The carbon tetrachloride solution from which **6** had been filtered (see above) was concentrated and distilled (short path, decomposition was apparent), giving an oil, bp 110–115° (1 mm). Redistillation through a 6-in. Vigreux column (bp 112–115°, 0.25 mm) gave an oil still contaminated with **12**. A sample collected 180°; decomposition is extensive) crystallized in needles from carbon tetrachloride–pentane at −25° after 3 weeks (mp 48–50°). The distillate crystallized when seeded. The analytical sample decomposed in transit, but gave for a parent peak *m/e* 242.1258 ± 0.0022 (calcd for $C_{11}H_{18}N_2O_4$, 242.1266); mass spectrum (70 eV) *m/e* (relative intensity) 242 (1), 199 (16), 184 (11), 166 (21), 140 (85), 109 (100), 108 (72), 107 (40); nmr (CCl_4) δ 5.18 (m, 1, vinyl), 4.93 (m, 1, vinyl), 4.61 (s, 1, vinyl), 3.75 (s, 3, OCH_3), 3.53 (s, 3, OCH_3), 2.55 (s, 6, $N(CH_3)_2$); ir (CCl_4) 5.72, 5.86, 6.29, 6.97 μ.

Dimethyloxalacetate Dimethylhydrazone (10).—A solution of 4.26 g of **2** in 20 ml of ether was dripped into 1.8 g of N,N-dimethylhydrazine in 10 ml of ether. When the refluxing had stopped the yellow solution was decanted from a black residue, concentrated, and distilled, bp 90–95° (0.5 mm), 2.1 g. This material was not obtained pure, but gave a parent having *m/e* 202.129 ± 0.037 (calcd for $C_8H_{14}N_2O_4$, 202.095); nmr (CCl_4) δ 3.73 (s, 3, OCH_3), 3.66 (s, 3, OCH_3), 3.57 (s, 2, CH_2), 2.88 (s, 6, $N(CH_3)_2$; ir 5.78–5.87, 6.35, 6.93 μ; uv (CH_3OH) maximum 291 nm (ϵ 6.3×10^3). This material had spectral properties identical with that isolated from reaction of **1** and **2** by tlc on silica gel which destroys **9**) followed by vpc on a 10 ft × 0.25 in. 10% FFAP column. The presence of **10** in the reaction mixtures was demonstrated by nmr of the methylene chloride solution before any work-up.

Methyl Dimethylacetylenedicarboxylate N,N-Dimethylhydrazide.—When 4.26 g (0.03 mol) of **1** and 1.80 g (0.03 mol) of N,N-dimethylhydrazine were allowed to react in 15 ml of methanol at −30° for 7 hr, 2.3 g of a solid, mp 170–193 dec, was isolated after evaporation. Two crystallizations from chloroform gave colorless rods: mp 200° dec; nmr ($CDCl_3$) δ 7.05 (s, 1, NH), 3.94 (s, 3, OCH_3), 3.50 (s, 6, $N(CH_3)_2$); ir ($CHCl_3$) 3.0 (w, broad), 5.78, 6.04, 6.20 μ.

Acetone dimethyl 2-aminomaleate imine (13) was isolated in small amounts by collection from a 10 ft × 0.25 in. 10% SE-30 vpc column when **9** was injected. Thermal decomposition of **9** in a flow system (230–265°) or neat (250°) gave only traces of **13**: nmr (CCl_4) δ 5.91 (s, 1, vinyl H), 3.77 (s, 3, OCH_3), 3.67 (s, 3, OCH_3), 1.98 (6, $NCCH_3)_2$); ir (CCl_4) 5.73, 5.89, 6.32 μ; uv (CH_3OH) 282 nm (ϵ 8.8×10^3); mass spectrum (70 eV) *m/e* (relative intensity) 199 (3), 167 (12), 141 (13), 137 (13), 123 (149), 109 (100), 108 (31), 183 (13).

Registry No.—**1**, 762-42-5; **2**, 13483-31-3; **6**, 19987-67-8; **7**, 19988-62-6; **9**, 19988-63-7; **10**, 19987-68-9; **11**, 19987-69-0; **13**, 19988-64-8.

Acknowledgment.—We thank the Petroleum Research Fund and the Wisconsin Alumnia Research Foundation for support of this work.

Cycloaddition Reactions of Isocyanates. The Addition of Sulfonyl Isocyanates to Carbodiimides[1]

HENRI ULRICH, B. TUCKER, F. A. STUBER, AND A. A. R. SAYIGH

The Upjohn Company, Donald S. Gilmore Research Laboratories, North Haven, Connecticut 06473

Received January 6, 1969

The polar cycloaddition reaction of arenesulfonyl isocyanates (**1**) with dialkylcarbodiimides (**2**) gives rise to the formation of six-membered ring cycloadducts **6** and **8**. The latter compound arises from interception of an acyclic polar 1:1 adduct by arenesulfonylalkylcarbodiimide (**9**), which is generated *via* an exchange sequence. Simultaneous cycloaddition of **1**, **2**, and **9** forms cycloadducts **6**, **8**, and **12**. Cycloadduct **12** is a 2:1 adduct of **9** and **2**. All cycloadducts readily thermolyze above 100° to lose alkyl isocyanate and give arenesulfonylcarbodiimides in good yield.

The cycloaddition reactions of arenesulfonyl isocyanates with double-bonded substrates often occur in a stepwise fashion.[1-4] The initially generated acyclic 1:1 adducts can undergo ring closure to produce four-membered ring cycloadducts or they can be intercepted by a double bond containing dipolarophile to yield six-membered ring cycloadducts. The possibility of interception is enhanced if the lifetime of the acyclic 1:1 adduct is increased by effective delocalization of the generated charges. In the arenesulfonyl isocyanate–dialkylcarbodiimide system delocalization of the generated charges in the initially formed acyclic adducts can occur readily, and since sulfonylheterocumulenes are excellent dipolarophiles the six-membered ring cycloadducts are obtained exclusively. The elucidation of structure of the six-membered ring cycloadducts is complicated by the ambident character of the generated acyclic 1:1 adducts and by the possibility of addition across either one of the double bonds in the heterocumulene substrates.

On mixing of equimolar amounts of arenesulfonyl isocyanate (**1**) and dialkylcarbodiimides (**2**), with or without a solvent, an immediate reaction occurs, as evidenced by the appearance of two double-bond absorptions at 1869 (medium) and 1724 cm^{-1} (strong),

(1) Part of this work appeared as a communication: H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Amer. Chem. Soc.*, **90**, 528 (1968).

(2) W. Bartmann, *Chem. Ber.*, **100**, 2938 (1967).

(3) E. J. Moriconi and W. C. Crawford, *J. Org. Chem.*, **33**, 370 (1968).

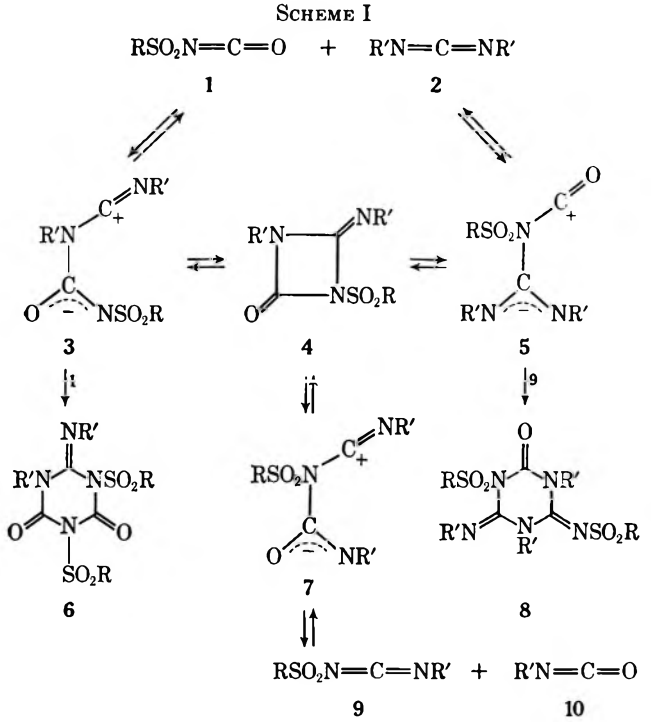
(4) R. Gompper, A. Studeneer, and W. Elsner, *Tetrahedron Lett.*, 1019 (1968).

respectively. The initially observed bands gradually disappear and cycloadducts **6** and **8** can be isolated from the reaction mixture.[5] If **2** is added slowly to excess **1**, the yield of cycloadduct **6** is significantly increased, indicating that **6** results from interception of **3** by **1**. The strong absorption band at 1724 cm^{-1} is indicative of an acyclic 1:1 adduct, as evidenced by the fact that the polar 1:1 adduct, generated by addition of *p*-toluenesulfonyl isocyanate to pyridine,[6] has a strong ir absorption at 1724 cm^{-1}.

The formation of the acyclic 1:1 adducts can also be observed by nmr spectroscopy. For example, immediately after mixing *p*-toluenesulfonyl isocyanate and *t*-butylmethylcarbodiimide in carbon tetrachloride the N-methyl signal of the carbodiimide is shifted from δ 2.9 to 3.32 ppm, indicating attachment of the isocyanato group to the less sterically hindered nitrogen adjacent to the methyl group. The broad signal at 3.32 ppm gradually decreases and new broad N-methyl signals appear at approximately 2.9 and 3.7 ppm. Simultaneously, new *t*-butyl signals at approximately 1.45 ppm are formed. Cycloadduct **6** (R = 4-$CH_3C_6H_4$; R′ = CH_3, *t*-C_4H_9) shows the N-methyl signal at 3.28 and the *t*-butyl signal at 1.48 ppm. The observed broad N-methyl signals may be indicative of formation of mixtures of acyclic and cyclic adducts.

The structure of cycloadduct **8** is rather interesting because it is formed by interception of the acyclic adduct **5** by **9**, the latter being generated *via* an exchange sequence (Scheme I). Since formation of **4**

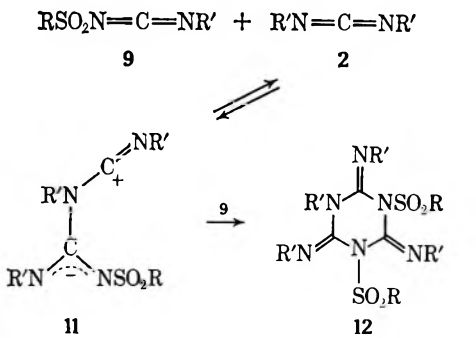
SCHEME I



is a stepwise process, ring opening may also occur in a stepwise fashion. Four acyclic 1:1 adducts are visualized, three of which are shown in Scheme I. The one not depicted also gives rise to formation of **9** and **10**. Of course, the acyclic 1:1 adduct **5** can be formed directly from **1** and **2**, but the simultaneous occurrence of the exchange reaction seems to indicate the intermediacy of **4**.[7] The ir absorption at 1869 cm^{-1} may in fact be caused by **4** or the isomeric 1:1 cycloadduct resulting from addition of the C=O bond of **1** across the C=N bond in **2**. The formation of **9** and **10** from the cycloadducts **6** and **8** is unlikely because the six-membered ring compounds are stable at room temperature.

If equimolar amounts of **1**, **2**, and **9** are combined at room temperature cycloadducts **6** and **8** are isolated from the reaction mixture. In addition, a new six-membered ring cycloadduct **12** is isolated, arising from the reaction of **9** with **2**. When 2 mol of **9** is mixed with 1 mol of **2**, cycloadduct **12** is formed almost exclusively (Scheme II), which verifies the mode of formation of **12**.

SCHEME II



The sulfonylheterocumulenes **1** and **9** are far better substrates than **2** and **10**, which is readily explained by the enhanced electrophilicity of the center carbon atoms in their cumulative double-bond arrangement. As a result the ir absorption due to alkyl isocyanate (**10**) can be observed in the mother liquor (isocyanates **1** and **10** can be differentiated by ir spectroscopy). Likewise, **1** and **9** are far better dipolarophiles than **2** and **10** as evidenced by their preferred reaction with the acyclic 1:1 adducts. Of course, reaction of **4** with **1** and **9** can also produce the cycloadducts **6** and **8**. However, Huisgen and his coworkers[8] have shown in a different system (azomethine–diphenylketene), in which 1:1 and 2:1 cycloadducts could be isolated, that the four-membered ring cycloadduct does not undergo reaction with the substrates.

The cycloadducts **6** show characteristic ir absorptions in $CHCl_3$ solution at 1754, 1721, and 1672 cm^{-1} which is in line with the proposed structure. The previously[1] proposed isomeric structure is being ruled out because of absence of $RSO_2N{=}C$ stretching vibration. The mass spectrum of **6** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}) shows the expected molecular ion at *m/e* 600. The major fragments observed are the ionized thermal degradation products (*i.e.*, *m/e* 278, 206, 197, and 125). The formation of the ion at *m/e* 125, $[C_6N_{11}NCO]^+$, also seems to rule out the previously proposed structure.

Hydrolysis of **6** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}) in 5% sodium hydroxide (to which a small amount of acetone is added to assure solubility) yields the intermediate guanidine derivative **13**, which is solvolyzed

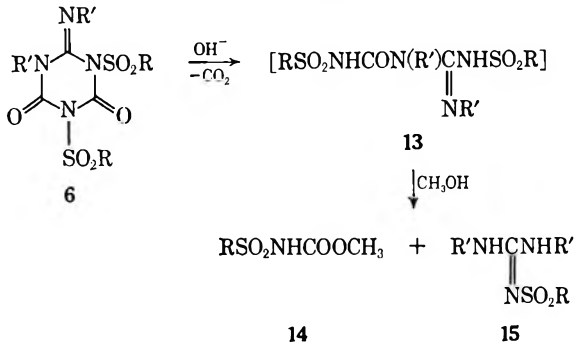
(5) We had assigned an isomeric structure for compound **6** in our preliminary communication.

(6) M. Seefelder, *Chem. Ber.*, **96**, 3243 (1963).

(7) W. Neumann and P. Fischer [*Angew. Chem.*, **74**, 801 (1962)] have postulated that the exchange reaction of isocyanates and carbodiimides involves **4** as the intermediate.

(8) R. Huisgen, B. A. Davis, and M. Morikawa, *ibid.*, **80**, 802 (1968).

SCHEME III



by methanol to the known compounds **14** and **15** (Scheme III).

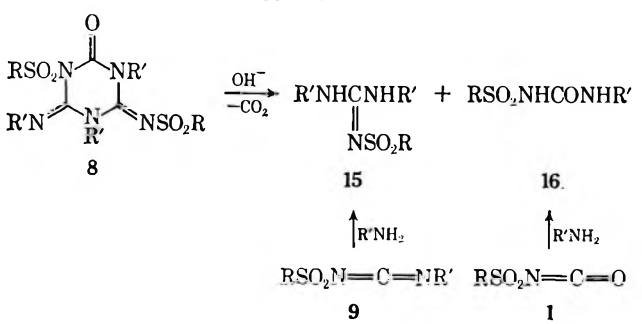
The carbamate **14** was compared with an authentic sample prepared from **1** (R = 4-$CH_3C_6H_4$) and methanol. Likewise, 1,3-dicyclohexyl-2-*p*-toluenesulfonylguanidine (**15**, R = 4-$CH_3C_4H_4$; R′ = C_6H_{11}) was synthesized independently (see Scheme IV).

The ir spectra of cycloadducts **8** in $CHCl_3$ solution differ from **6** because in addition to the C=O and C=N stretching vibrations at 1718 and 1672 cm^{-1} a strong RSO_2N=C stretching vibration at 1582–1558 cm^{-1} is observed. In **15** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}) the RSO_2N=C absorption occurs at 1587–1550 cm^{-1}.

The mass spectrum of **8** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}) shows a molecular ion at *m/e* 681. Breakdown of the six-membered ring leads to four possible stable fragments which all have been observed. The intensities of these ions are small compared with those of the ions obtained by ejection of substituents from the molecular ion. One path of degradation starts by the loss of C_6H_9 to form an immonium ion and follows by two successive losses of C_6H_{10}. Additional fragmentation sequences are shown in Scheme V.

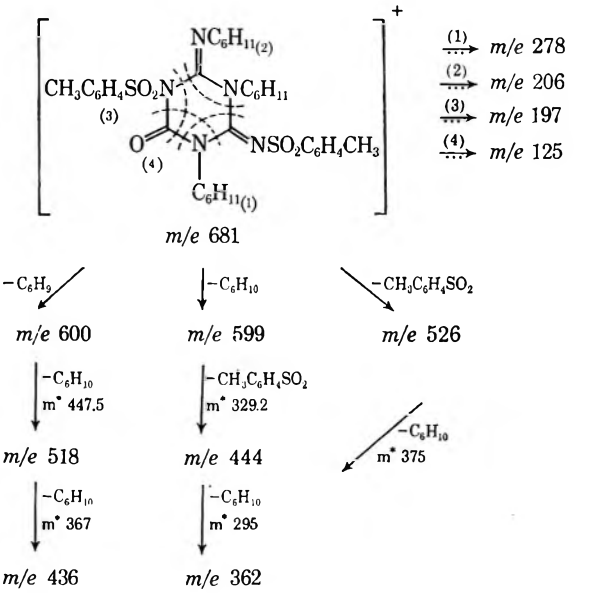
Basic hydrolysis of **8** in 5% aqueous sodium hydroxide–acetone affords approximately equal amounts of **15** and **16**, and the hydrolysis products were identified by comparison with independently prepared authentic samples (Scheme IV).

SCHEME IV



Cycloadduct **12** shows only one double-bond absorption in the ir at 1655 cm^{-1} (C=N) which is in line with the proposed structure. The mass spectrum of **12** shows major fragments at *m/e* 278 and 206, which are again ions of the expected thermal fragments. Although this cycloadduct is quite stable toward base hydrolysis, attempted oxidation with CrO_3 in acetic acid again yields **15** as the only isolable product most likely arising from acid hydrolysis of **12**.

SCHEME V



All cycloadducts undergo fragmentation above 100° and the occurring equilibria can be shifted toward formation of the sulfonylcarbodiimide (**9**) by slow removal of the lowest boiling species (R′NCO). Thus dialkylcarbodiimides (**2**) are converted into arenesulfonyl alkylcarbodiimides (**9**) by means of arenesulfonyl isocyanate (**1**).

$$\underset{\mathbf{1}}{RSO_2N{=}C{=}O} + \underset{\mathbf{2}}{R'N{=}C{=}NR'} \longrightarrow \underset{\mathbf{9}}{RSO_2N{=}C{=}NR'} + \underset{\mathbf{10}}{R'NCO}\uparrow$$

The obtained yields are quite good and most likely deviate from theory because of reaction of **1** with the generated **9**. This new one-step method of synthesis of arenesulfonylalkylcarbodiimides (**9**), which are precursors of antidiabetic 1-arenesulfonyl-3-alkylureas, has the advantage over previously described methods,[9–12] that no handling of noxious gases (phosgene or chlorine) is required.

Experimental Section

Melting and boiling points are uncorrected. Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ir spectra were determined using a Beckman IR-8 spectrophotometer. Nmr spectra were obtained from samples in $CDCl_3$ or CCl_4 solutions with a Varian A-60 instrument using tetramethylsilane as the internal standard. Mass spectra were determined using a MS-12 mass spectrograph.

Reaction of *p*-Toluenesulfonyl Isocyanate and Dicyclohexylcarbodimide. A. Stoichiometric Amounts.—To 6.18 g (0.03 mol) of dicyclohexylcarbodiimide dropwise and with stirring 5.19 g (0.03 mol) of *p*-toluenesulfonyl isocyanate is added at 24–52°. After standing for 3 hr complete reaction has occurred as evidenced by ir spectroscopy. The reaction mixture is added to CCl_4 to precipitate 1.2 g (13.3%) of **1,3-di-*p*-toluenesulfonyl-5-cyclohexyl-6-cyclohexylimino-1,3,5-triazine-2,6-dione** (**b**, R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}): mp 170–172°; ir (KBr) 1769, 1748 (C=O), 1690 cm^{-1} (C=N); nmr ($CDCl_3$) δ 2.4 (s, 6, $2CH_3$-C_6H_4); mass spectrum (70 eV) *m/e* (relative intensity) 600 (0.1), 278 (0.9), 206 (6.1), 197 (26.5), 155 (52.5), 125 (11.4), 91 (100).

(9) H. Ulrich and A. A. R. Sayigh, *Angew. Chem. Intern. Ed., Engl.*, **3**, 639 (1964).

(10) H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Tetrahedron*, **22**, 1565 (1966).

(11) B. Anders and E. Kühle, *Angew. Chem. Intern. Ed., Engl.*, **4**, 430 (1965).

(12) R. Neidlein, W. Haussmann, and E. Heukelbach, *Chem. Ber.*, **99**, 1252 (1966).

Anal. Calcd for $C_{29}H_{36}N_4O_6S_2$: C, 57.93; H, 6.03; N, 9.32. Found: C, 57.63; H, 5.94; N, 9.27.

Evaporation of CCl_4 at room temperature and trituration of the residue with methanol precipitates 6.9 g (67.6%) of **1-*p*-toluenesulfonyl-3,5-dicyclohexyl-2-cyclohexylimino-4-*p*-toluenesulfonylimino-1,3,5-triazin-6-one** (**8**, R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}): mp 180–182°, ir (KBr) 1750 (C=O) 1690, 1580 cm^{-1} (C=N); nmr ($CDCl_3$) δ 2.43, 2.48 (2 s, 6, $2CH_3C_6H_4$); mass spectrum (70 eV) *m/e* (relative intensity) 681 (0.1), 526 (11.5), 518 (40), 444 (22.3), 197 (13.0), 155 (52), 125 (6.3), 91 (100).

Anal. Calcd for $C_{35}H_{47}N_5O_5S_2$: C, 61.59; H, 6.94; N, 10.25. Found: C, 61.34; H, 7.01; N, 9.97.

If the reaction is conducted in benzene (50% concentration) the obtained yields are **6** = 21.3%, **8** = 42%. In CCl_4 (50% concentration) the yields based on the same isolation technique are **6** = 27%, **8** = 52%.

B. Excess *p*-Toluenesulfonyl Isocyanate.—To 19.7 g (0.1 mol) of *p*-toluenesulfonyl isocyanate slowly and dropwise 6.18 g (0.03 mol) of dicyclohexylcarbodiimide is added at 24–48°. The reaction is complete after 15 min as indicated by the absence of N=C=N vibration stretching at 2165 cm^{-1} in the infrared. Addition to CCl_4 precipitates 13.45 g (75%) of **6** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}), mp 165–168°.

Reaction of *p*-Toluenesulfonyl Isocyanate, *p*-Toluenesulfonylcyclohexylcarbodiimide, and Dicyclohexylcarbodiimide.—To 2.78 g (0.01 mol) of *p*-toluenesulfonylcyclohexylcarbodiimide in 4.2 g of CCl_4, 1.97 g (0.01 mol) of *p*-toluenesulfonyl isocyanate is added. No reaction is noted as evidenced by infrared spectroscopy. Addition of 2.06 g (0.01 mol) of dicyclohexylcarbodiimide dissolved in 2 g of CCl_4 causes an exothermic reaction. Filtration yields 0.3 g of **6** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}), mp 164–165°. Evaporation of the solvent under vacuum and crystallization from methanol yields 1.0 g of **12** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}), mp 120°, and from the methanol 0.4 g of **8** (R-4 = $CH_3C_6H_4$; R′ = C_6H_{11}) is isolated.

1-Cyclohexyl-3,5-di-*p*-toluenesulfonyl-1,3,5-triazine-2,4,6-tricyclohexylimine (**12**, **R = 4-$CH_3C_6H_4$**; **R′ = C_6H_{11}**).—A mixture of 2 g (0.007 mol) of *p*-toluenesulfonylcyclohexylcarbodiimide and 1.44 g (0.007 mol) of dicyclohexylcarbodiimide in 7 g of CCl_4 is kept at room temperature for several hours. Trituration with methanol yields 2.7 g (99%, calculated on *p*-toluenesulfonylcyclohexylcarbodiimide) of **12** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}): mp 123–124°; ir (KBr) 1655 cm^{-1} (C=N); nmr ($CDCl_3$) δ 2.41 (s, 6, 2 $CH_3C_6H_4$).

Anal. Calcd for $C_{41}H_{53}N_6O_4S_2$: C, 64.52; H, 7.66; N, 11.01. Found: C, 64.27; H, 7.61, N, 10.96.

A 0.3-g sample of **12** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}) upon heating in 5 ml of glacial acetic acid in the presence of 0.2 g of CrO_3 yields a small amount of **15** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}), mp 152–154°.

Reaction of *p*-Chlorobenzenesulfonyl Isocyanate and Dicyclohexylcarbodiimide.—To 20.6 g (0.1 mol) of dicyclohexylcarbodiimide in 100 ml of benzene dropwise and with stirring 21.75 g (0.1 mol) of *p*-chlorobenzenesulfonyl isocyanate is added rapidly at 28–40°. Evaporation of the solvent under vacuum and trituration of the residue with diethyl ether yields 9.6 g (30%) of **1,3-di-*p*-chlorobenzenesulfonyl-5-cyclohexyl-6-cyclohexylimino-1,3,5-triazine-2,6-dione** (**6**, R = 4-ClC_6H_4; R′ = C_6H_{11}): mp 150–153°; ir ($CHCl_3$) 1754, 1721 (C=O), 1672 cm^{-1} (C=N).

Anal. Calcd for $C_{27}H_{30}Cl_2N_4O_6S_2$: C, 50.55; H, 4.68; N, 8.74. Found: C, 50.49; H, 5.11; N, 8.60.

On standing 8.75 g (24%) of **1-p-chlorobenzenesulfonyl-3,5-dicyclohexyl-2-cyclohexylimino-4-*p*-chlorobenzenesulfonylimino-1,3,5-triazin-6-one** (**8**, R = 4-ClC_6H_4; R′ = C_6H_{11}) [mp 163–165°; ir ($CHCl_3$) 1718 (C=O), 1672, and 1582–1558 cm^{-1} (C=N)] is obtained.

Anal. Calcd for $C_{33}H_{41}Cl_2N_5O_5S_2$: C, 55.03; H, 5.73; N, 9.11. Found: C, 55.18, H, 6.17; N, 9.11.

If 10.3 g (0.05 mol) of dicyclohexylcarbodiimide is added to 21.75 g (0.1 mol) of *p*-chlorobenzenesulfonyl isocyanate over a period of 4 min at 26–38°, 18.5 g (57.8%) of **6** (R = 4-ClC_6H_4; R′ = C_6H_{11}), mp 150–153°, is obtained.

Reaction of *p*-Toluenesulfonyl Isocyanate and *t*-Butylmethylcarbodiimide.—To 5.6 g (0.05 mol) of *t*-butylmethylcarbodiimide in 100 ml of benzene dropwise and with stirring 9.85 g (0.05 mol) of *p*-toluenesulfonyl isocyanate is added over a period of 2 min, at 25–32°. Evaporation of the solvent under vacuum and trituration with diethyl ether and benzene yields 2.95 g (25%) of **1,3-di-*p*-toluenesulfonyl-4-*t*-butylimino-5-methyl-1,3,5-triazine-2,6-dione** (**6**, R = 4-$CH_3C_6H_4$; R′ = CH_3, *t*-C_4H_9): mp 145–146°; ir ($CHCl_3$) 1754, 1718 (C=O), 1681 cm^{-1} (C=N): nmr ($CDCl_3$) δ 1.48 [s, 9, $(CH_3)_3C$], 2.32 (s, 3, $CH_3C_6H_4$), 2.5 (s, 3, $CH_3C_6H_4$), 3.28 (s, 3, CH_3N).

Anal. Calcd for $C_{22}H_{26}N_4O_6S_2$: C, 52.17; H, 5.13; N, 11.07. Found: C, 51.89; H, 5.28; N, 10.84.

Hydrolysis of 1,3-Di-*p*-toluenesulfonyl-5-cyclohexyl-6-cyclohexylimino-1,3,5-triazine-2,6-dione (**6**, **R = 4-$CH_3C_6H_4$**; **R′ = C_6H_{11}**),—An amount of 4.0 g (0.067 mol) of the triazine derivative is suspended in a mixture of 65 ml of 5% aqueous NaOH and 30 ml of acetone, and the reaction mixture is gently heated until a clear solution is obtained. On cooling a white precipitate is formed which is collected and triturated with dilute HCl. Recrystallization from methanol yields 1.4 g (56%) of 1,3-dicyclohexyl-2-*p*-toluenesulfonylguanidine (**15**, R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}): mp 158–160° (lit.[13] mp 161°); ir ($CHCl_3$) 1587–1550 cm^{-1} (C=N). Evaporation of the methanol affords 0.8 (52%) of methyl *p*-toluenesulfonylcarbamate (**14**, R = 4-$CH_3C_6H_4$), mp 111–113° (lit.[14] mp 115°), after recrystallization from CCl_4.

In one experiment a minute amount of the precursor of **14** and **15** (*i.e.*, **13**, R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}), mp 120–123°, was isolated as evidenced by the C=O and C=N absorption at 1701 and 1592 cm^{-1}, respectively.

1,3-Dicyclohexyl-2-*p*-toluenesulfonylguanidine (**15**, **R = 4-$CH_3C_6H_4$**; **R′ = C_6H_{11}**).—To 0.278 g (0.001 mol) of *p*-toluenesulfonylcyclohexylcarbodiimide in 3 ml of chloroform 0.1 g (0.001 mol) of cyclohexylamine is added dropwise at 22–40°. Evaporation of the solvent and recrystallization from methanol yields 0.23 g (60.8%) of **15** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}), mp 160–162°.

Hydrolysis of 1-*p*-Toluenesulfonyl-3,5-dicyclohexyl-2-cyclohexylimino-4-*p*-toluenesulfonylimino-1,3,5-triazin-6-one (**8**, **R = 4-$CH_3C_6H_4$**; **R′ = C_6H_{11}**).—An amount of 2.0 g (0.003 mol) of **8** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}) is heated in a mixture of 65 ml of 5% aqueous NaOH and 65 ml of acetone until most of the suspended material becomes soluble. The reaction mixture is filtered and 150 ml of water is added to precipitate 0.85 g (75%) of **15** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}), mp 157–159°. Neutralization of the filtrate with hydrochloric acid precipitates 0.66 g (75%) of 1-*p*-toluenesulfonyl-3-cyclohexylurea, **16** (R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}), mp 175–177° (lit.[15] mp 172–173°).

The urea derivative was compared with a sample obtained from **1** (R = 4-$CH_3C_6H_4$) and cyclohexylamine; the mixture melting point showed no depression and the ir spectra were superimposable.

***p*-Toluenesulfonylisopropylcarbodiimide** (**9**, **R = 4-$CH_3C_6H_4$**; **R′ = *i*-C_3H_7**).—An amount of 6.46 g of a mixture of cycloadducts obtained from *p*-toluenesulfonyl isocyanate and diisopropylcarbodiimide is dissolved in 35 ml of o-dichlorobenzene and slowly distillation over a Vigreux column affords a distillate containing a solution of isopropyl isocyanate and diisopropylcarbodiimide in *o*-dichlorobenzene. Vacuum distillation of the residue yields 3.27 g of *p*-toluenesulfonylisopropylcarbodiimide: bp 168° (0.1 mm); $n^{27}D$ 1.5380; ir ($CHCl_3$) 2165 cm^{-1} (SO_2-N=C=N).

Upon addition of a sample of *p*-toluenesulfonylisopropylcarbodiimide to wet acetone 1-*p*-toluenesulfonyl-3-isopropylurea, mp 147–148° (lit.[16] mp 146°), is obtained.

***p*-Toluenesulfonyl-*n*-butylcarbodiimide** (**9**, **R = 4-$CH_3C_6H_4$**; **R′ = *n*-C_4H_9**).—To 4.62 g (0.03 mol) of di-*n*-butylcarbodiimide in 30 ml of benzene dropwise and with stirring 5.91 g (0.03 mol) of *p*-toluenesulfonyl isocyanate is added at 27–41°. Evaporation of the benzene yields 10.5 g of a mixture of cycloadducts as evidenced by complete disappearance of the cumulative double-bond absorptions and appearance of C=O and C=N bond stretching vibrations. Heating under vacuum in an oil bath results in complete fragmentation with formation of 1.3 g (43.7%) of *n*-butyl isocyanate, bp 114–116°, and 4.27 g (42.7%) of *p*-toluenesulfonyl-*n*-butylcarbodiimide, bp 155–158° (0.2 mm) [lit.[9,10] bp 159–162° (0.2 mm)].

***p*-Toluenesulfonylcyclohexylcarbodiimide** (**9**, **R = 4-$CH_3C_6H_4$**;

(13) W. V. Farrar, *J. Chem. Soc.*, 856 (1965).

(14) C. F. Boehringer and Soehne G.m.b.H., Netherlands Patent Appl. 6,603,399 (1966); *Chem. Abstr.*, **66**, 55245 (1967).

(15) H. Ruschig, G. Kroger, W. Aumüller, H. Wagner, R. Weyer, A. Bänder, and J. Scholz, *Arzneim.-Forsch.*, **8**, 448 (1958); *Chem. Abstr.*, **53**, 1317 (1959).

(16) R. Gryglewski, *Dissertations Pharm.*, **9**, 205 (1957); *Chem. Abstr.*, **52**, 6248 (1958).

R′ = C_6H_{11}).—An amount of 8.06 g of a mixture of cycloadducts, obtained from *p*-toluenesulfonyl isocyanate and dicyclohexylcarbodiimide, is heated in 50 ml of *o*-dichlorobenzene with simultaneous distillation of most of the solvent. Vacuum distillation of the residue yields 4.6 g of *p*-toluenesulfonylcyclohexylcarbodiimide: bp 203–206° (0.3 mm); mp 50–52° (lit.[17] mp 52°); ir ($CHCl_3$) 2151 cm^{-1} ($SO_2N{=}C{=}N$).

(17) Farbenfabriken Bayer A. G., Netherlands Patent Appl. 6,413,827 (1966); *Chem. Abstr.*, **64**, 19506 (1966).

Registry No.—**6**, R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}, 19978-05-3; **6**, R = 4-ClC_6H_4; R = C_6H_{11}, 19978-06-4; **6**, R = 4-$CH_3C_6H_4$; R′ = CH_3, *t*-C_4H_9, 19978-07-5; **8**, R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}, 19978-08-6; **8**, R = 4-ClC_6H_4; R′ = C_6H_{11}, 19978-09-7; **9**, R = 4-$CH_3C_6H_4$; R′ = *i*-C_3H_7, 19978-10-0; **12**, R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}, 19978-11-1; **15**, R = 4-$CH_3C_6H_4$; R′ = C_6H_{11}, 908-18-9.

Diaziridinones (2,3-Diazacyclopropanones). II.[1a] Synthesis, Properties, and Reactions[1b]

FREDERICK D. GREENE, JOHN C. STOWELL, AND WILLIAM R. BERGMARK

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

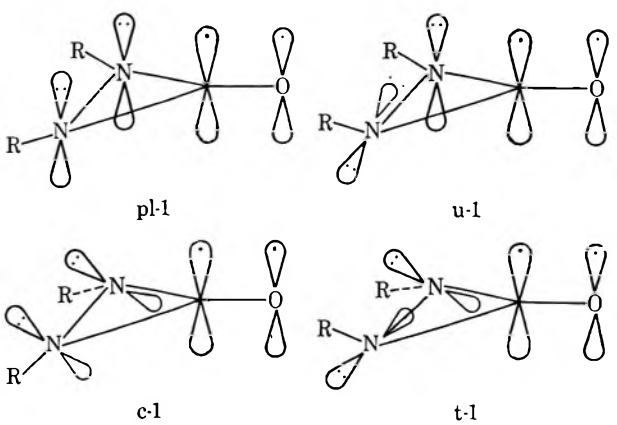
Received August 26, 1968

Reaction of 1-chloro-1,3-di-*t*-alkylurea with potassium *t*-butoxide in *t*-butyl alcohol effects ring closure to a diaziridinone **1**, a new three-membered ring heterocycle. Spectral data indicate a *trans* orientation for the substituents attached to the nitrogen atoms. The diaziridinones are reactive toward acids, only moderately reactive toward a range of nucleophiles, and function as mild oxidizing agents toward thiols, phenols, enols, and some hydrazines. The acids studied include hydrogen chloride, picric acid, benzoic acid, and formic acid with resultant ring opening of diaziridinone and formation of substituted carbazates **8a**, c–e. A second method of formation of diaziridinones is found in the regeneration of **1a** by the action of potassium *t*-butoxide on 2,3-di-*t*-butylcarbazyl chloride **8a**. Studies of the action of nucleophiles on di-*t*-butyldiaziridinone include *t*-butoxide, *t*-butyl alcohol, methoxide, and methanol (ring opening to alkyl carbazates **8b** and **8f**), isopropylamine (ring opening to substituted semicarbazide **10**), and hydrazine (ring opening and conversion to carbohydrazide). Di-*t*-butyldiaziridinone is reduced by benzylthiol (or ethanethiol) to 1,3-di-*t*-butylurea and benzyl disulfide (or ethyl disulfide). Diaziridinone **1a** is reduced to the urea rapidly by ascorbic acid and by phenylhydrazine and, more slowly, by phenol and by 2,4,6-tri-*t*-butylphenol. *t*-Butylhydroxylamine reacts with **1a** both by nucleophilic attack at carbonyl carbon with ring opening giving carbazate **17**, and by oxidation–reduction giving di-*t*-butylurea and 2-methyl-2-nitrosopropane. The reactions described here constitute a new method for the formation of a nitrogen–nitrogen bond, hydrazo, and azo compounds. They also provide new routes to substituted carbazates and semicarbazides. Of special interest in the chemistry of diaziridinones is the balance between nucleophilic ring opening with cleavage of the carbonyl carbon–nitrogen bond and oxidation–reduction ring opening with reductive cleavage of the nitrogen–nitrogen bond.

In a search for new methods for the formation of the nitrogen–nitrogen bond, we have examined the effect of strong bases on 1-chloroureas, in analogy to the Favorskii reaction. Reaction occurs, a nitrogen–nitrogen bond *is* formed, and (contrary to our original expectations) the resulting 2,3-diazacyclopropanones (hereafter called diaziridinones)[2] are, in a number of instances, isolable and moderately stable compounds. This paper describes the synthesis, evidence on structure, and a number of reactions of this new class of compounds (Scheme I).[3]

In all cases examined to date, this route has succeeded only when both R and R′ are tertiary alkyl groups. The 1-chloroureas may be isolated and characterized but in general good yields of diaziridinones are obtained without isolation of this species. Diaziridinones may also be prepared by reaction of the 1-chlorourea in pentane with potassium but yields have been lower than by the *t*-butoxide route (Scheme II[4]).

Stereochemistry.—Possible spatial arrangements for the R groups of **1** are shown in pl-1, u-1, c-1, and t-1. In both pl-1 and u-1, a nitrogen lone pair of electrons is in a p orbital conjugated with the carbonyl π system.



The usual delocalization effect in amides is a shift from the value of 1710 cm^{-1} observed in simple ketones to 1650–1690 cm^{-1} (1660–1695 cm^{-1} for ureas). An amide in which delocalization from nitrogen to oxygen is disallowed by the orthogonality of the orbitals, quinuclidone-2,[5] shows carbonyl absorption at 1750 cm^{-1}, ~40 cm^{-1} *higher* than a simple ketone. Cyclo-

(1) (a) Part I: F. D. Greene and J. C. Stowell, *J. Amer. Chem. Soc.*, **86**, 3569 (1964). (b) Financial support from the National Science Foundation (Grant No. GP-5527) is gratefully acknowledged.

(2) For recent reviews of three-membered ring heterocyclic compounds, see (a) E. Schmitz, "Dreiringe mit Zwei Heteroatomen," Springer-Verlag, Berlin, 1967; (b) I. Lengyel and J. C. Sheehan, *Angew. Chem.*, **80**, 27 (1968); *Angew. Chem. Intern. Ed. Engl.*, **7**, 25 (1968).

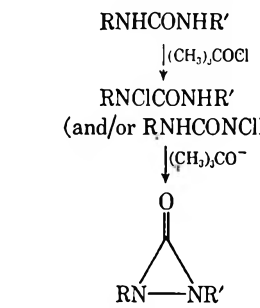
(3) The methods are analogous to those used to prepare α-lactams; see ref 2b and H. E. Baumgarten, J. F. Fuerholzer, R. D. Clark, and R. D. Thompson, *J. Amer. Chem. Soc.*, **85**, 3303 (1963).

(4) Nmr values are in parts per million downfield from TMS.

(5) H. Pracejus, M. Kehlen, H. Kehlen, and M. Matschiner, *Tetrahedron*, **21**, 2257 (1965).

SCHEME I

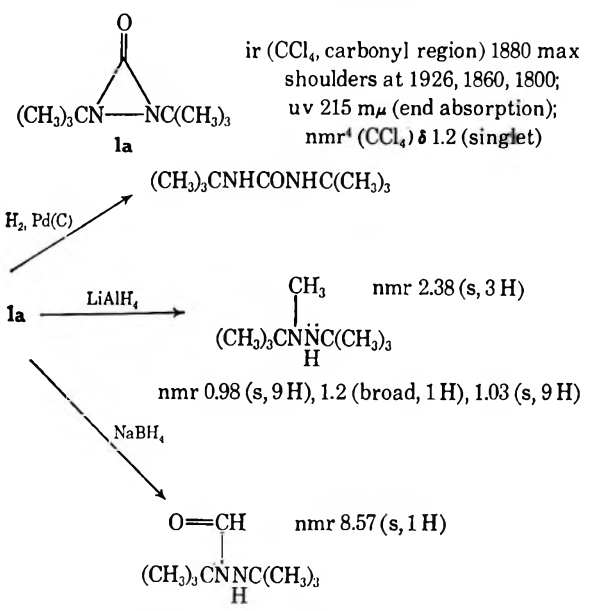
SYNTHESIS OF DIAZIRIDINONES



1a, R = R′ = *t*-butyl
b, R = R′ = *t*-amyl
c, R = R′ = *t*-octyl
d, R = R′ = 2-methyl-3-phenyl-2-propyl
e, R = *t*-butyl; R′ = *t*-octyl

SCHEME II

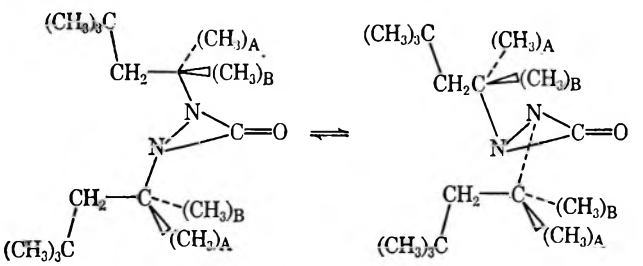
EVIDENCE ON STRUCTURE, DI-*t*-BUTYLDIAZIRIDINONE



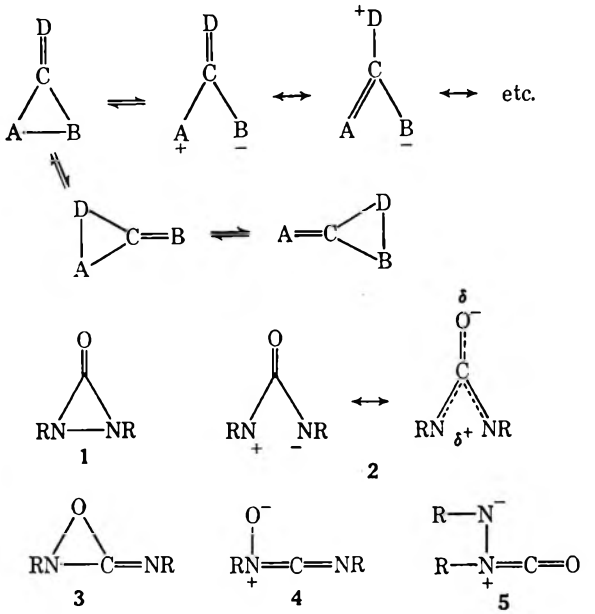
propanones have values of 1813–1840 cm^{-1},[6] aziridinones 1837–1850 cm^{-1},[2b] and diaziridinones 1855–1880 cm^{-1}. These data suggest a decreased amount of nitrogen lone pair delocalization in diaziridinones in comparison with urea, and favor structures c-1 and t-1 over pl-1 and u-1. Structure c-1, with two large groups eclipsed, would be expected to be less stable than t-1.

The dipole moment of di-*t*-butyldiaziridinone measured in benzene solution at 24° is 2.6 D. This may be compared with values of 3.47 D for tetramethylurea,[7] 5.1 D for 1,3-dimethylurea,[7] 2.76 D for cyclobutanone,[7] and 4.78 D for di-*n*-butylcyclopropenone.[8]

Further evidence on stereochemistry is found in the temperature dependence of the nmr spectrum of di-*t*-octyldiaziridinone. Below 30°, the methyl groups on the carbon atoms attached to the nitrogen atoms appear as two equal peaks ($\Delta\delta$ = 7 Hz). On heating to 40°, the doublet coalesces to a single sharp peak, corresponding to a ΔF^* of ~16 kcal/mol. The magnitude of this energy barrier seems too great to be ascribed to hindered rotation around an sp^3 C–N bond. The nmr observations are, however, in accord with interconversion of the two optical antipodes of *trans*-**1** *via* "slow" inversion about both nitrogen atoms.[9] The nmr spectrum of di-*t*-butyldiaziridinone is a sharp singlet, unchanged over the range examined, −40 to +150°.



Reactions of Diaziridinones. General Considerations.—The diaziridinones present several aspects of interest. As a three-ring system possessing an exocyclic multiple bond, a diaziridinone has the possibility of "ring–chain" isomerism[10] and small-ring isomerism (**1**, **2**, **3**, **4**, **5**).[11]



Each of the alternatives **2**–**5** fails in some respects to accommodate the physical and chemical evidence presented in this paper, which strongly favors structure **1** for the ground state of diaziridinones. Detailed consideration of the role these structures (*e.g.*, **2**–**5**) may play in the chemistry of diaziridinones is deferred to a later paper in which reactions requiring their involvement are described. In the reactions outlined

(6) (a) N. J. Turro and W. B. Hammond, *J. Amer. Chem. Soc.*, **88**, 3673 (1965); (b) J. F. Pazos and F. D. Greene, *ibid.*, **89**, 1030 (1967).

(7) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963.

(8) R. Breslow, T. Eicher, A. Krebs, R. A. Peterson, and J. Posner, *J. Amer. Chem. Soc.*, **87**, 1320, 1326 (1965).

(9) See R. S. Atkinson, *Chem. Commun.*, 676 (1968), and references cited therein; L. W. Reeves, *Advan. Phys. Org. Chem.*, **3**, 187 (1965).

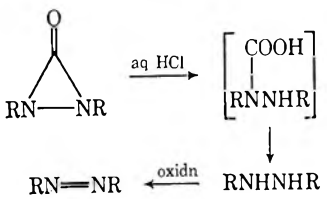
(10) J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954); see also A. W. Fort, *J. Amer. Chem. Soc.*, **84**, 2620 (1962), and references therein.

(11) See E. F. Ullman and W. J. Fanshawe, *ibid.*, **83**, 2379 (1961); J. P. Chesick, *ibid.*, **85**, 2720 (1963); J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 5091 (1966).

below, however, one should bear in mind the possibility of involvement of these forms.

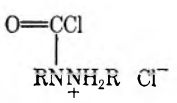
Reactivity.—The diaziridinones studied to date have a tertiary alkyl group on each nitrogen. The compounds are moderately stable to heat and light, generally insensitive to water, only moderately reactive toward a range of nucleophiles, reactive toward acids, and undergo a number of interesting reactions with certain reducing agents. Most of the exploratory work on reactivity has been carried out on di-*t*-butyldiaziridinone.

Effects of Acids.—Diaziridinones undergo facile ring opening with acid. Aqueous hydrochloric acid effects ring opening and decarboxylation (eq 1). The resulting hydrazine has been isolated in 90% yield from di-*t*-butyldiaziridinone. This sequence constitutes a useful route to hydrazines and the corresponding azo compounds, readily obtained by a subsequent oxidation. It may be of special use in the synthesis of unsymmetrical tertiary azo compounds;[12] the symmetrical ones may be prepared by the action of IF_5 on the tertiary alkyl primary amine.[13]

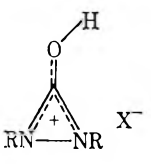


(1)

Treatment of **1a** with dry hydrogen chloride in pentane affords an immediate precipitate. This material is soluble in chloroform and shows two singlets for the *t*-butyl groups in the nmr and a carbonyl band at 1750 cm^{-1} (Nujol) on which grounds it is assigned structure **6**, the hydrochloride of the carbazyl chloride, rather than a protonated diaziridinone **7**. The free



6

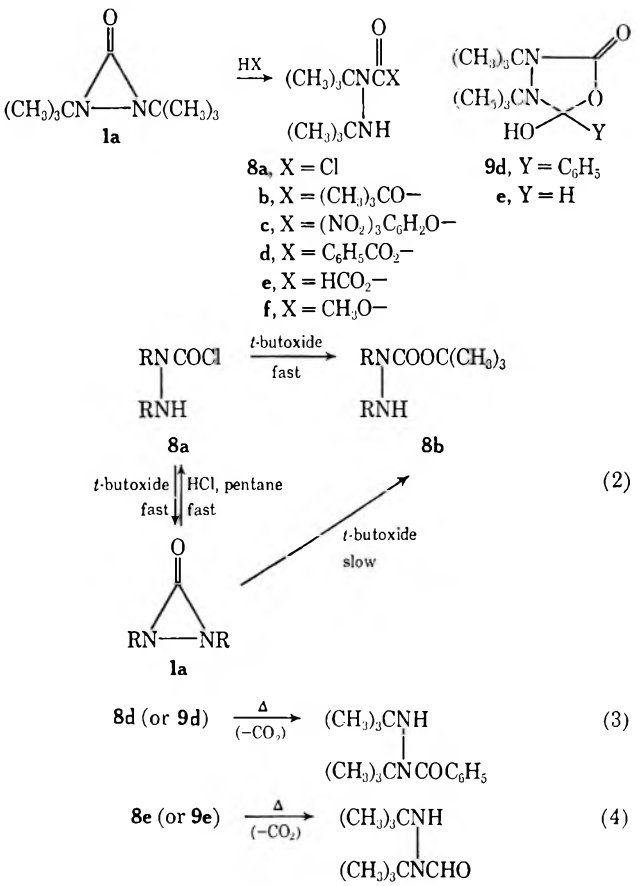


7

carbazyl chloride, **8a**, is easily obtained from **6**. Treatment of **8a** with *t*-butyl alcohol–potassium *t*-butoxide effects rapid conversion to a mixture of the *t*-butyl carbazate **8b** (25%) and **1a** (45%), eq 2. Here, **8b** is formed directly from **8a** and not from **1a**; reaction of **1a** with *t*-butoxide is a much slower reaction (see next section).

The conversion of the carbazyl chloride to the diaziridinone (eq 2) constitutes a second method of preparation of this ring system.

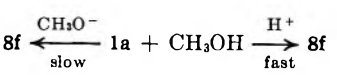
Picric acid effects rapid conversion of **1a** to the picryl carbazate **8c**. Reaction with less acidic phenols such as phenol itself or alkyl-substituted phenols



takes an entirely different course, an oxidation–reduction reaction, and is discussed in a later section of this paper.

Reaction of **1a** with benzoic acid proceeds more slowly than with picric acid, and affords **8d** (or its cyclic tautometric form, **9d**). Upon heating, **8d** (or **9d**) is converted to 1-benzoyl-1,2-di-*t*-butylhydrazine with loss of carbon dioxide (eq 3). In view of the reducing properties of formic acid, its action on **1a** was examined. The reaction proceeds as with benzoic acid.

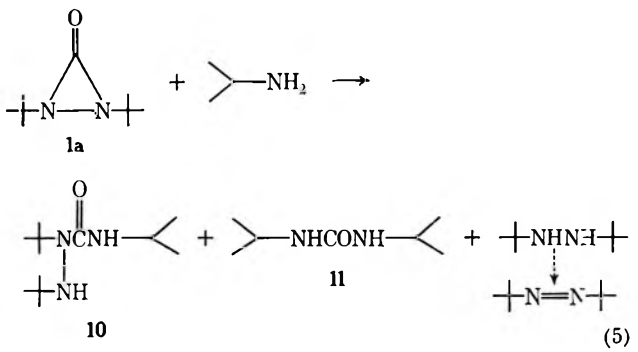
Effect of Nucleophiles. A. Attack at Carbonyl Carbon.—Diaziridinones are rather sluggish toward nucleophilic attack at the carbonyl carbon atom. Reflux for 16 hr in *t*-butyl alcohol containing potassium *t*-butoxide is required to effect 50% ring opening of **1a** to *t*-butyl 2,3-di-*t*-butylcarbazate, **8b**. As expected, reaction with methanol–methoxide is more rapid (complete conversion to the methyl carbazate after 40 min at reflux in 0.4 *M* CH_3ONa–CH_3OH). Far more rapid, however, is the conversion of **1a** to **8f** by acid catalysis in place of base catalysis.



Reaction of **1a** with a few amines has been examined. From the reaction of equimolar amounts of isopropylamine and **1a** at 25° for 96 hr were obtained 1,2-di-*t*-butyl-4-isopropylsemicarbazide, **10** (35%), 1,3-diisopropylurea, **11** (25%), and 2,2′-dimethyl-2,2′-azopropane (from air oxidation of the corresponding hy-

(12) Primary and secondary 1,2-disubstituted hydrazines are accessible from the corresponding azines. A variety of symmetrical 1,2-disubstituted hydrazines also may be prepared *via* the 1,2-dialkyl sulfuric acid diamides: R. Ohme and E. Schmitz, *Angew. Chem.*, **77**, 429 (1965).

(13) T. E. Stevens, *J. Org. Chem.*, **26**, 2531 (1961); S. F. Nelson and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 137 (1966).

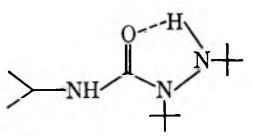


1a

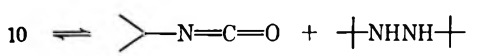
10 11

(5)

drazine liberated in the reaction), eq 5. It is of interest that **10** competes so well with the diaziridinone for isopropylamine. 1-*t*-Butyl-3-isopropylurea, a compound comparable with **10** in the degree of steric hindrance at carbonyl carbon, was inert toward the amine. The greater reactivity of **10** may be associated with intramolecular catalysis *via* **10a**. Alternatively, it may



10a



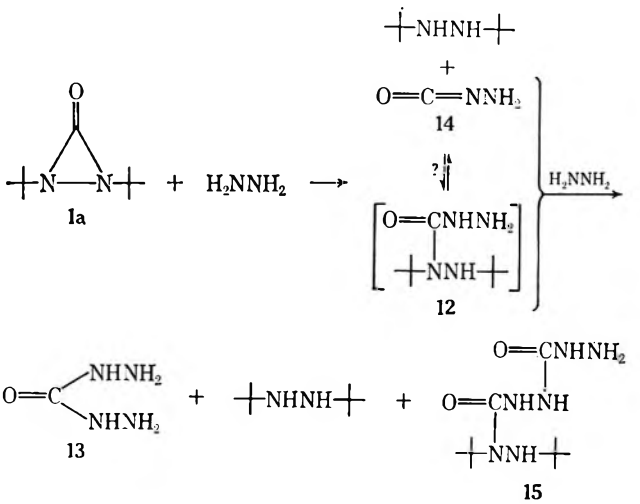
be due to dissociation of **10** into isopropyl isocyanate and 1,2-di-*t*-butylhydrazine, followed by reaction of the isocyanate with the isopropylamine.[14] A choice between these paths might be made by use of a secondary amine in place of isopropylamine, in that the species corresponding to **10** would then lack the NH necessary for dissociation into an isocyanate. However, diethylamine was too unreactive toward the diaziridinone, precluding the desired mechanistic distinction. Under the conditions of the **1a**–isopropylamine reaction, aniline does not react with **1a**.

The slowness of nucleophilic attack at the carbonyl carbon of diaziridinones requires comment. The data relevant to structure provide a strong indication that diaziridinones have stereochemistry t-1. The *trans*-oriented *t*-alkyl groups provide considerable steric hindrance to the carbonyl carbon. Nucleophilic attack at carbonyl carbon is much faster with *trans*-2,3-di-*t*-butylcyclopropanone[6b] than with di-*t*-butyldiaziridinone. Thus, delocalization of nitrogen lone pair electrons to the carbonyl group in t-1, although of diminished value in comparison with acyclic amides and ureas, is still of consequence. A second factor leading to reduced reactivity of the diaziridinone compared with the cyclopropanone may be repulsion between a nitrogen lone pair and the nucleophile as it approaches the carbonyl carbon.

B. Reaction with Hydrazines.—Hydrazines interact with diaziridinones in three ways: (1) nucleophilic attack at carbonyl carbon, (2) oxidation of the hydrazine and reduction of the diaziridinone to the corresponding urea, (3) rearrangement of the diaziridinone to an aziridinecarboxamide (1-carbamoylaziridine). Some information on the first two categories is presented in this paper. The third category (and its relation to the second) is treated in detail in part III of this series.[15]

Reaction of **1a** with hydrazine in a 1:1 molar ratio affords carbohydrazide **13** (23%) and a compound to which is assigned structure **15** (25%), 1-(2,3-di-*t*-butylcarbazyl)carbohydrazide, along with di-*t*-butylhydrazine and unchanged **1a**. Reaction of **1a** with a tenfold excess of hydrazine affords **13** (93%) and di-*t*-butylhydrazine (72%). In neither case was the intermediate **12** obtained. Here also, as with the question of **10** and isopropylamine discussed above, the basis for the apparent reactivity of **12** with hydrazine is not known; the main possibilities are intramolecular catalysis or dissociation to **14** and di-*t*-butylhydrazine.[14] The insolubility of carbohydrazide **13** in the reaction medium is suggestive that formation of **15** from **12** + **14** may be preferred over **13** + **1a** (or **12**) (Scheme III).

SCHEME III



1a 14 12 13 15

C. Oxidation–Reduction Reactions with Nucleophiles.—In marked contrast to the reaction of hydrazine with di-*t*-butyldiaziridinone **1a**, in which the initial step is simple nucleophilic attack at carbonyl carbon, phenylhydrazine reacts with **1a** to give 1,3-di-*t*-butylurea, benzene, and nitrogen (eq 6). In general, both aliphatic- or aromatic-substituted hydrazines undergo oxidation–reduction reactions with the diaziridinone **1a** rather than nucleophilic attack at carbonyl carbon. This aspect has been examined for a series of diaziridinones.[15]

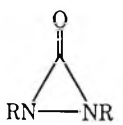
Reaction of **1a** with thiols also involves over-all oxidation–reduction affording urea **16** and disulfide (eq 7, R′ = benzyl and ethyl) rather than nucleophilic ring opening. Reaction of ethanethiol and **1a** in pentane at 25° for 20 days afforded di-*t*-butylurea (33%), diethyl disulfide (34%), and recovered **1a** (54%).

Most phenols also effect reduction of **1a** to the urea (eq 8). As noted earlier, the highly acidic phenol, picric acid, behaves like other acids toward **1a** and effects ring opening (eq 9) to picryl carbazate **8b** with no evidence of reduction of **1a** to the urea. The enediol, ascorbic acid, effects rapid reduction of **1a** to the urea (eq 10).

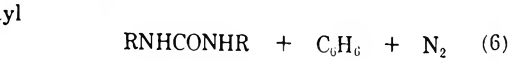
(14) T. Mukaiyama and Y. Hoshino, *J. Amer. Chem. Soc.*, **78**, 1946 (1956).

(15) F. D. Greene, W. R. Bergmark, and J. G. Pacifici, *J. Org. Chem.*, **34**, 2263 (1969).

The oxidizable nucleophile, *t*-butylhydroxylamine, reacts with **1a** by both oxidation–reduction, giving 2-methyl-2-nitrosopropane in 40% yield and di-*t*-butylurea in 30% yield, and by nucleophilic ring opening, giving a 1:1 adduct assigned structure **17** (eq 11) on the basis of the physical data and its clean pyrolysis (eq 12) to 2,2′-dimethyl-2,2′-azopropane, carbon dioxide, and *t*-butylamine (the latter two react to give *t*-butylammonium *t*-butylcarbamate **18**).



1a, R = *t*-butyl

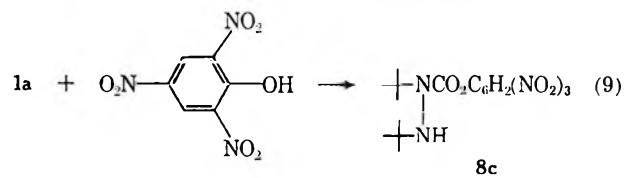


(6)

16, R = *t*-butyl

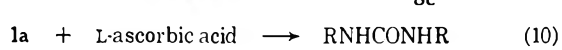
(7)

(8)



(9)

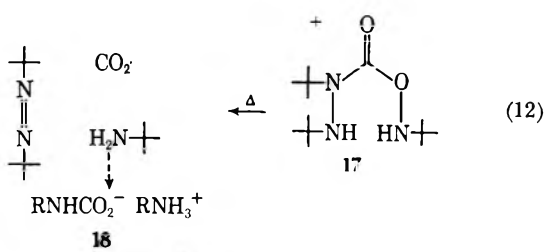
8c



(10)

(11)

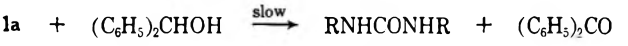
30% 40%



(12)

17

18



(13)

The possibility of oxidation–reduction with **1a** and an alcohol was examined briefly with benzhydrol. After several days at reflux in benzene, one obtains benzophenone, di-*t*-butylurea, and unchanged **1a** (eq 13). The possible product of nucleophilic attack at carbonyl carbon was not observed. As noted earlier, methanol reacts slowly with **1a** to afford the methyl carbazate **8f**.

Effect of Trapping Agents.—If diaziridinones underwent ring opening to forms such as **2**, one might hope to capture the resulting 1,3-dipolar species by appropriate dipolarophiles.[16] No evidence for trapped products has been found from experiments in which **1a** was heated in cyclohexene, cyclopentadiene, or norbornylene. Efforts to obtain 1:1 adducts with maleic anhydride or tetracyanoethylene also were unsuccessful. (However, **1a** and TCNE do afford an immediate yellow color in methylene chloride which slowly darkens.) Either the ring-opened species are too hindered to undergo cycloaddition with the reagents used to date, or they are not formed to an adequate extent.

(16) See R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968), and references cited therein.

Experimental Section

All melting points are corrected. All melting points of 1,3-di-*t*-butylurea were taken in tubes sealed under vacuum. Nuclear magnetic resonance spectra were determined at 60 Mc; signals are reported in parts per million (ppm) downfield from tetramethylsilane. Gas–liquid partition chromatographic analyses (glpc) were performed on Aerograph Models 200 and A-700 (Autoprep) using a helium carrier gas and thermal conductivity detectors with the following columns: column A [a 6 ft × 0.25 in. aluminum tube packed with 20% (w/w) silicone oil "SE-30" on a 60/80 mesh Chromosorb W diatomite support employing a flow rate of 65 cc/min; column B [a 10 ft × 0.25 in. aluminum tube packed with 80/100 Linde Molecular Sieves 5A]; column E [a 4 ft × 0.25 in. aluminum tube packed with 20% (w/w) Apiezon M hydrocarbon grease on a Chromosorb P diatomite base washed to pH 7–8 employing a flow rate of 65 ml/min. All identifications (unless otherwise noted) of glpc components were made by the identity with an authentic sample of both retention time and ir spectrum of a collected sample. All quantitative analyses were made by the internal standardization method unless otherwise noted. Assessment of error was obtained in several of the analytical series by matching two or more standard solutions against each other. Error was found to be ±2%.

Preparation of Diaziridinones.—*t*-**Octylamine** had bp 139°, n^{25}D 1.4220 (lit.[17] bp 139°, n^{25}D 1.4222); *t*-**amylamine** had bp 78–79°, n^{25}D 1.3950 (lit.[18] bp 77°, n^{20}D 1.3990). **1,3-Di-*t*-butylurea** was prepared by the action of phosgene on a benzene solution of the amine: mp 243–244° (sealed tube) (lit.[19] mp 242°); ir (CCl_4) 1680, 1650 cm^{-1}. **1,3-Di-*t*-octylurea** was prepared by exchange of *t*-octylamine with urea:[20] mp 150–151° (lit.[20] mp 152°); nmr ($CDCl_3$, all singlets) 1.00 (18 H), 1.30 (12 H), 1.72 (4 H), 4.35 (two NH). **1,3-Bis(2-methyl-3-phenyl-2-propyl)-urea** had mp 181–182° (lit.[21] mp 184–185°). *t*-**Butyl isocyanate** had bp 85–86°, n^{25}D 1.3842 (lit.[22] bp 85.5°).

1,3-Di-*t*-amylurea was prepared by a method adapted from one of Pepesch and Schroeder.[23] Recrystallization from ethanol–water gave the urea in 69% yield: mp 220–220.5°; ir ($CHCl_3$) 3425 b, 1675 s, 1505 s, 1380 m, 1375 sh, m, 1360 cm^{-1}; nmr ($CDCl_3$) 0.90 triplet (6 H, J = 7.5 Hz), 1.29 singlet (12 H), 1.75 quartet (4 H, J = 7.5 Hz), 4.30 broad singlet (two NH).

Anal. Calcd for $C_{11}H_{24}N_2O$: C, 65.95; H, 12.08; N, 13.99. Found: C, 65.90; H, 12.28; N, 13.90.

1-*t*-Butyl-3-isopropylurea.—To a stirring solution of 4.28 ml (2.95 g, 0.05 mol) of isopropylamine (Eastman) in 50 ml of dry benzene was added 4.58 ml (3.97 g, 0.04 mol) of *t*-butyl isocyanate. The mixture was stirred 12 hr, solvent evaporated, and the solid was recrystallized (ethanol–water) to give 5.00 g (79%) of long, white needles: mp 203–204°; ir ($CHCl_3$) 1665 cm^{-1} s.

Anal. Calcd for $C_8H_{18}N_2O$: C, 60.71; H, 11.46. Found: C, 60.75; H, 11.71.

1-*t*-Butyl-3-*t*-octylurea [mp 153–154° (lit.[20] mp 154–155°)] was prepared in the same way.

1,3-Di-*t*-butyl-1-chlorourea.—A procedure similar to that used by Chalsty and Israelstam[24] to prepare monochlorourea was applied. 1,3-Di-*t*-butylurea (5.00 g, 0.0290 mol) was dissolved in 25 ml of methanol, and *t*-butyl hypochlorite (3.15 g, 0.0290 mol) was added with stirring. After 15 min of stirring, the methanol was removed on a rotatory evaporator to give an oil. The oil was recrystallized twice at −78° from 20 ml of pentane to give 5.09 g (85%): mp 30–31°; ir (CCl_4) 1690, 1505 cm^{-1}; nmr (CCl_4, all singlets) 1.33 (9 H), 1.43 (9 H), 5.48 (1 H, broad). The compound decomposes at room temperature but may be stored at −20°.

(17) J. J. Ritter and J. Kalish, *J. Amer. Chem. Soc.*, **70**, 4048 (1948); J. J. Ritter and P. P. Minieri, *ibid.*, **70**, 4045 (1948).
(18) W. Haaf, *Chem. Ber.*, **96**, 3359 (1963).
(19) A. Bühler and H. E. Fierz-David, *Helv. Chim. Acta*, **26**, 2123 (1943).
(20) N. Bortnick, L. S. Luskin, M. D. Hurwitz, and A. W. Rytina, *J. Amer. Chem. Soc.*, **78**, 4358 (1956).
(21) C. Mentzer, French Patent 973,665 (1951).
(22) W. Siefken, *Ann.*, **562**, 75 (1949).
(23) V. Papesch and E. F. Schroeder, *J. Org. Chem.*, **16**, 1879 (1951).
(24) J. S. Chalsty and S. S. Israelstam, *J. S. Afr. Chem. Inst.*, **9**, 37 (1956).

Anal. Calcd for $C_9H_{19}N_2OCl$: C, 52.29; H, 9.26; N, 13.55; Cl, 17.15. Found: C, 52.52; H, 9.25; N, 13.27; Cl, 17.36.

1-Chloro-1,3-di-*t*-octylurea was prepared from 1,3-di-*t*-octylurea and *t*-butyl hypochlorite by the same method:[24] yield 43.5% after two recrystallizations from pentane at −78°; mp 31.5°; ir (CCl_4) 3450 sp, 1690 cm^{-1} s; nmr (CCl_4, all singlets) 1.01 (18 H), 1.35 (6 H), 1.45 (6 H), 1.68 (2 H), 1.90 (2 H).

Anal. Calcd for $C_{17}H_{35}ClN_2O$: C, 64.02; H, 11.08; Cl, 11.13; N, 8.78. Found: C, 64.13; H, 10.90; Cl, 11.14; N, 8.91.

Di-*t*-butyldiaziridinone (1a). A. From Potassium Metal.—Potassium metal (3.0 g, 0.077 g-atom) was dispersed in hot toluene; the toluene was removed under reduced pressure and was replaced with 90 ml of pentane. 1,3-Di-*t*-butyl-1-chlorourea (8.00 g, 0.0387 mol) was added and the mixture was heated to reflux under nitrogen with vigorous stirring for 1.25 hr. The mixture was filtered and the solid washed with pentane. The combined filtrate and washings were distilled to remove the pentane and then the residue was distilled at 0.3 mm and 25° to give 2.75 g (48%): mp 0–1°; $n^{26}D$ 1.4267; d^{29} 0.871 g/ml; ir (CCl_4) 1926 weak, 1880 strong, 1862 strong, and 1800 cm^{-1} weak; nmr (CCl_4) 1.20 (s); uv (end absorption) 215 mμ (ε 1190) (not a maximum).

Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.45; mol wt, 170.3. Found: C, 63.38; H, 10.74; N, 16.47; mol wt, 178 ± 10 (cryoscopic in cyclohexane).

B. From Potassium *t*-Butoxide. The Preferred Method.—*t*-Butyl hypochlorite, 53.4 ml (48.6 g, 449 mmol), was added dropwise with stirring over a 5-min period to a viscous, creamy suspension of 77.4 g (440 mmol) finely ground 1,3-di-*t*-butylurea in 350 ml of *t*-butyl alcohol distilled from sodium metal. The mixture was protected from the light. At the end of the addition, all the urea had gone into solution. To the clear pale yellow-green solution was added over a 10-min period a solution of potassium *t*-butoxide in *t*-butyl alcohol [prepared from 19.9 g (0.51 g-atom) of potassium metal in 500 ml of *t*-butyl alcohol] under nitrogen. Stirring was continued for 10 min. The mixture was poured into 3 l. of water and extracted with three 500-ml portions of pentane. The combined pentane extracts were extracted with three 1-l. portions of water and dried (K_2CO_3). (The use of $MgSO_4$ and standing for several hours results in some acid-catalyzed addition of *t*-butyl alcohol to **1a** to give carbazate **8b**.) Pentane was removed on a steam bath and the diaziridinone was distilled on a spinning-band column at 58–59° (8 mm): yield 68.6 g, 90%; $n^{26}D$ 1.4236.

Di-*t*-amyldiaziridinone (1b), by method B, gave a 75% yield: bp 66.5–67.5° (8 mm); ir (CCl_4) 1920 sh, 1860 s, none at 1500–1800 nor at 3200–3600, 1460, 1380, 1365, 1075 cm^{-1}; nmr (CCl_4) 0.98 (t, 6 H, J = 7.5 Hz), 1.13 (s, 12 H), 1.60 (q, 4 H; J = 7.5 Hz); $n^{24}D$ 1.4440.

Anal. Calcd for $C_{11}H_{22}N_2O$: C, 66.62; H, 11.18; N, 14.13. Found: C, 66.78; H, 11.21; N, 14.18.

Di-*t*-octyldiaziridinone (1c), by method B, had $n^{26.2}D$ 1.4562; ir (CCl_4) 1870 s, b, none at 3100–3700, 1470, 1395 w, 1380 m, 1370 m, 1345 w, 1060 cm^{-1} m; nmr (CCl_4) 1.02 (S, 18 H), 1.58 (s, 4 H), and at 20.0° a broad doublet centered at 1.20 (12 H) with a separation of about 3 Hz; at 40° this doublet coalesces to a broad singlet at 1.20 which continues to sharpen with further rise in temperature; at 0° the doublets show a 7 Hz separation.

Anal. Calcd for $C_{17}H_{34}N_2O$: C, 72.28; H, 12.13; N, 9.92. Found: C, 72.57; H, 12.18; N, 9.71.

Bis(2-methyl-3-phenyl-2-propyl)diaziridinone (1d), by method B, had mp 43–44° (from pentane), ir (CCl_4) 1855 s; nmr (CCl_4) 1.10 (s, 12 H), 2.80 (s, 4 H), 7.13 (s, 10 H).

Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.30; H, 8.11; N, 8.62.

***t*-Butyl-*t*-octyldiaziridinone (1e)**, by method B, gave a 71% yield: bp 50–50.5° (0.1 mm); $n^{24.4}D$ 1.4450; nmr at 90° (benzene) 1.06 (s, 9 H), 1.18 (s, 9 H), 1.21 (s, 6 H), and 1.64 (s, 2 H); nmr at −16° (CCl_4) 1.07 (s, 9 H), 1.15, 1.20, 1.24 (singlets, a total of 15 H), and 1.62 (s, 2 H); ir ($CHCl_3$) 1855 cm^{-1} (s).

Anal. Calcd for $C_{13}H_{26}N_2O$: C, 68.98; H, 11.58; N, 12.38. Found: C, 69.04; H, 11.50; N, 12.39.

Dipole Moment of Di-*t*-butyldiaziridinone (1a).—The dipole moment of di-*t*-butyldiaziridinone was determined by the heterodyne beat method with an oscilloscope detector.[25] A value of 2.63 D was obtained with measurements at 24.0° from four benzene solutions from which the following mole fractions, densities, and dielectric constants were recorded: (a) 0.00937, 0.8725, 2.282; (b) 0.0195, 0.8734, 2.501; (c) 0.0421, 0.8730, 2.715; (d) 0.0577, 0.8737, 2.921.

Hydrogenation of Di-*t*-butyldiaziridinone.—The diaziridinone (26.7 mg, 0.157 mmol) was hydrogenated at 1 atm in 3 ml of ethyl acetate using 50 mg of 5% palladium-on-carbon catalyst. Filtration followed by evaporation of the ethyl acetate gave 25.9 mg (95.6%) of 1,3-di-*t*-butylurea, mp 240–242°, infrared spectrum identical with that of authentic material.

Lithium Aluminum Hydride Reduction of Di-*t*-butyldiaziridinone.—Di-*t*-butyldiaziridinone (1.00 g, 5.87 mmol) was added dropwise to a suspension of 0.60 g (0.016 mol) of lithium aluminum hydride in 50 ml of ether. The mixture began to reflux, and heat was applied to maintain refluxing for 30 min. A slight excess of water was added and the mixture was filtered. The solid was washed with ether, and the combined washings and filtrate were evaporated to give 0.90 g of clear oil. This was distilled at 0.3 mm and 25° to afford 0.794 g (85%) of 1,2-di-*t*-butyl-1-methylhydrazine, about 98% pure by gas chromatography. A sample, collected at 95°, showed $n^{25}D$ 1.4254; nmr (CCl_4) 0.98 (9 H), 1.03 (9 H), 1.2 (1 H, broad), 2.38 (s, 3 H).

Anal. Calcd for $C_9H_{22}N_2$: C, 68.29; H, 14.01; N, 17.70. Found: C, 68.24; H, 14.28; N, 18.02.

Sodium Borohydride Reduction of Di-*t*-butyldiaziridinone.—Sodium borohydride (151 mg, 4.00 mmol) and di-*t*-butyldiaziridinone (500 mg, 2.94 mmol) were heated at reflux in 2 ml of absolute ethanol for 1 hr. Water (3 ml) was added and refluxing was continued for 0.5 hr. This was added to 10 ml of water and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give a white solid. This was sublimed at 0.2 mm and 25° to yield 0.313 g (61.7%) of 1,2-di-*t*-butyl-1-formylhydrazine, mp 38–41°. Four successive sublimations raised the melting point to 42–43°: ir (CCl_4) 1670 cm^{-1}; nmr (CCl_4) 1.08 (s, 9 H), 1.37 (s, 9 H), 4.2 (1 H, broad), 8.57 (s, 1 H).

Anal. Calcd for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26; O, 9.29. Found: C, 62.87; H, 11.82; N, 16.04; O, 9.50.

Reaction of Di-*t*-butyldiaziridinone with Hydrogen Chloride.—Hydrogen chloride gas was bubbled into a solution of 1.00 g (5.86 mmol) of di-*t*-butyldiaziridinone in 50 ml of pentane for 10 min, giving a white precipitate. Water (5 ml) was added and the white precipitate dissolved. The pentane layer was separated, dried ($MgSO_4$), and evaporated to give 0.80 g (66%) of 2,3-di-*t*-butylcarbazyl chloride, ir (CCl_4) 1745 cm^{-1}. A sample distilled at 0.3 mm and 50° gave nmr 1.2 (s, 9 H), 1.43 (s, 9 H), 4.04 (1 H, broad), and a positive silver nitrate test. The acid chloride slowly decomposes to a white solid at room temperature.

A solution of the acid chloride (100 mg, 0.483 mmol) in 1 ml of carbon tetrachloride was treated with 400 mg (4.30 mmol) of aniline at room temperature giving an immediate precipitate. This was washed with water and recrystallized from ethanol–water to give 50 mg of diphenylurea: mp 241–242° (lit. mp 238–239°); ir (Nujol) 1640, 1590, 1540 cm^{-1}.

Reaction of 2,3-Di-*t*-butylcarbazyl Chloride with Potassium *t*-Butoxide.—2,3-Di-*t*-butylcarbazyl chloride (0.760 g, 3.68 mmol) was added dropwise to a solution of potassium *t*-butoxide prepared from 0.250 g (6.40 mg-atom) of potassium metal and 20 ml of *t*-butyl alcohol (distilled from sodium). After 10 min of stirring, the mixture was poured into 50 ml of water and extracted with pentane. The extract was washed with water, dried ($MgSO_4$), and evaporated to give a clear oil. An infrared spectrum showed carbonyl absorptions for only di-*t*-butyldiaziridinone and *t*-butyl 2,3-di-*t*-butylcarbazate. Distillation of the oil at 0.3 mm and 25° gave 0.20 g (45%) of the diaziridinone containing a small amount of the carbazate. Further distillation using a heat lamp gave 0.218 g (24%) of the carbazate (see following section) containing a small amount of the diaziridinone.

***t*-Butyl 2,3-Di-*t*-butylcarbazate.**—Di-*t*-butyldiaziridinone (0.50 g, 2.93 mmol) was added to a solution of potassium *t*-butoxide prepared from 0.30 g (7.68 mg-atom) of potassium metal and 25 ml of *t*-butyl alcohol (distilled from sodium) and heated to reflux for 16 hr. An infrared spectrum of the reaction solution showed carbonyl bands of about equal intensity for the diaziridinone and the carbazate. The *t*-butyl alcohol was removed on a rotary evaporator and the residue was extracted with ether. Evaporation of the ether left a residue which was distilled at 0.2 mm and 25° to give 0.284 g of a mixture of *t*-butyl alcohol, the

(25) D. P. Shoemaker and C. W. Garland, "Experiments in Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

diaziridinone, and the carbazate. The residue of this distillation was extracted with pentane, and the extract evaporated and distilled at 0.2 mm under a heat lamp to afford 0.192 g of *t*-butyl 2,3-di-*t*-butylcarbazate. A sample, collected by glpc at 135°, had n^{26}D 1.4320; ir (CCl_4) 1690 cm^{-1}; nmr (CCl_4) 1.02 (s, 9 H), 1.31 (s, 9 H), 1.48 (s, 9 H), 3.95 (1 H, broad).

Anal. Calcd for $C_{13}H_{28}N_2O_2$: C, 63.89; H, 11.55; N, 11.47. Found: C, 64.09; H, 11.49; N, 11.63.

1,2-Di-*t*-butylhydrazine. A. From *t*-Butyl 2,3-Di-*t*-butylcarbazate (8b).—To 9.40 g (38.4 mmol) of *t*-butyl 2,3-di-*t*-butylcarbazate was added with stirring 20 ml of 36% HCl (aqueous). Bubbling occurred for 30 min. The solution was stirred for an additional 30 min, made basic with sodium hydroxide solution (20% aqueous), and extracted four times with pentane (total pentane, 225 ml). The combined pentane extracts were washed with water and dried (K_2CO_3). Removal of the pentane yielded 5.01 g (91%) of crude 1,2-di-*t*-butylhydrazine. Glpc analysis at 150° (column E) indicated that pentane and 2,2'-dimethyl-2,2'-azopropane were impurities. Di-*t*-butylhydrazine purified by glpc has nmr (CCl_4) 1.15 ppm (singlet); ir (CCl_4) 3200–2400 b, 1475 m, 1450 m, 1385 m, 1365 m, 1210 m cm^{-1}; $n^{27.5}$D 1.4122.

Anal. Calcd for $C_8H_{20}N_2$: C, 66.60; H, 13.97; N, 19.42. Found: C, 66.52; H, 13.83; N, 19.61.

B. From Di-*t*-butyldiaziridinone (1a).—A total of 21.0 ml (18.3 g, 107.5 mmol) of 1a was added portionwise to 850 ml of 4.2% aqueous HCl. Stirring was continued for 30 min after CO_2 evolution ceased and a clear, homogeneous solution resulted (total time about 2 hr). All further operations were performed under a nitrogen atmosphere. The solution was made pH 12 by addition of saturated aqueous NaOH and extracted quickly with two 250-ml portions of ether; the ether solution was dried (K_2CO_3), solvent was removed, and the residue was distilled on a spinning-band column, affording 14 g, bp 137–138°, yield 90%, which was immediately transferred into tubes which were sealed under vacuum.

The use of a large volume of dilute acid was important; when 60 ml of 36% aqueous HCl was used in the above procedure only a low yield of the hydrazine was recovered (23%).

Reaction of Benzoic Acid and Di-*t*-butyldiaziridinone.—Benzoic acid (0.716 g, 5.86 mmol) and di-*t*-butyldiaziridinone (1.00 g, 5.86 mmol) were dissolved in 15 ml of benzene and heated at reflux under nitrogen for 1 hr. All of the diaziridinone was consumed as shown by infrared analysis. The benzene was removed on a rotary evaporator to afford an oil. Addition of 3 ml of pentane caused crystallization of a white solid which was filtered and washed with pentane. This gave 0.473 g (28%) of **8–9d**, mp 145–147° dec. Three recrystallizations from ether gave mp 152–154° dec; ir (CCl_4) 1655 cm^{-1}; nmr (CCl_4) 1.08 (s, 9 H), 1.6 (s, 9 H), 7.45 (m 5 H), 11.8 (1 H, broad).

Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.72; H, 8.27; N, 9.58. Found: C, 65.69; H, 8.37; N, 9.42.

The pentane washings and filtrate were combined and cooled to −20° to afford 0.367 g (25%) of white needles, mp 62–69°. Sublimation at 55° and 0.2 mm afforded 1-benzoyl-1,2-di-*t*-butylhydrazine: mp 72–74°; ir (CCl_4) 1650 cm^{-1}; nmr (CCl_4) 1.04 (s 9 H), 1.11 (s, 9 H), 4.89 (broad, 1 H), 7.5 (m, 5 H).

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.49; H, 9.84; N, 11.40.

The last pentane filtrate contained at least two unidentified compounds with infrared absorptions at 1700 and 1760 cm^{-1}.

Another reaction heated at reflux for 5 hr afforded an 87% yield of 1-benzoyl-1 2-di-*t*-butylhydrazine and none of the compound of mp 152–154°. A reaction heated at reflux for 30 min afforded a 42% yield of the compound of mp 152–154°.

Reaction of Formic Acid with Di-*t*-butyldiaziridinone.—A solution of 0.67 ml (0.82 g 17.6 mmol) of formic acid (Baker reagent) in 15 ml of ether was added dropwise over a 2-hr period to a stirring, ice-bath cooled solution of 3.44 ml (3.00 g, 17.6 mmol) of diaziridinone 1a in 15 ml of ether. The stirring was continued for 12 hr while the ice bath was allowed to melt and warm to room temperature. A white precipitate was collected by filtration, washed, and dried: yield 2 20 g; mp 136° dec with gas evolution. Removal of the ether afforded an additional 1.10 g isolated as above, mp 139° dec (gas evolution). Recrystallization of the first fraction ($CHCl_3/CCl_4$) afforded 985 mg, mp 146° dec (gas evolution), identified as formyl 2,3-di-*t*-butylcarbazate (**8e**): ir ($CHCl_3$) 3400–3000 b, 2875 m, 2730 m, 2590 m, 1685 s, 1305 s, 1340 m, 1180 cm^{-1} m; nmr ($CDCl_3$, all singlets) 1.51 (18 H), 8.15 (1 H), 12.2 (1 H). Total yield of carbazate **8e** was 3.30 g (86.3%). The assignment of structure **8e** is preferred over **9e** on the basis of nmr and ir evidence: the single CH proton appears at 8.15 ppm which is reasonable for a formate –CHO, but not for the –CHOH of **9e**. Characteristic –CHO combination bands also appear in the ir region at 2875 and 2730 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55 53; H, 9.32; N, 12.96. Found: C, 55.63; H, 8.99; N, 13.26.

The filtrate obtained after removal of all the ether contained diaziridinone 1a. After 48 hr under high vacuum a mixture of two components (tlc on silica gel) remained with ir (film) 1775 s and 1715 cm^{-1} s. When the above reaction was carried out without solvent or cooling, an exothermic reaction took place with the liberation of gas. The resulting solid–liquid mixture was separated into a pentane-insoluble fraction, 982 mg, mp 123–125° dec, with gas evolution, which was identified as crude formyl 2,3-di-*t*-butylcarbazate, **8e**, by tlc on silica gel and by ir. Distillation of the pentane-soluble fraction at 25° and 0.02 mm afforded 691 mg of 1-formyl-1,2-di-*t*-butylhydrazine.

Pyrolysis of Formyl 2,3-Di-*t*-butylcarbazate (8e).—A solution of 792 mg (3.66 mmol) of carbazate **8e** in 20 ml of benzene and 20 ml of toluene was refluxed for 15 hr. Gas was given off. After removal of the toluene and benzene the residue was heated to 160° for 1 hr and then sublimed at 0.02 mm at 50° to yield 408 mg (59%) of pure 1-formyl-1,2-di-*t*-butylhydrazine: mp 42.5–43.5°; mmp 42.5–43.5°; ir spectrum identical with that of the authentic sample.

Picryl 2,3-Di-*t*-butylcarbazate (8c).—Picric acid (0.500 g, 2.94 mmol) was dissolved in 70 ml of anhydrous ether and di-*t*-butyldiaziridinone (0.670 g, 2.94 mmol) was added dropwise, causing an immediate darkening of the yellow color. The ether was evaporated to give a yellow solid. Recrystallization from 10 ml of carbon tetrachloride gave 1.00 g (85.5%), mp 144–148°. Two more recrystallizations afforded yellow plates: mp 147–149° dec; ir (CCl_4) 1750, 1610, 1555 cm^{-1}; nmr (CCl_4) 1.19 (s, 9 H), 1.44 (s, 9 H), 3.95 (broad, 1 H), 8.95 (s, 2 H).

Anal. Calcd for $C_{15}H_{21}N_5O_8$: C, 45.11; H 5.30; N 17.54. Found: C, 44.90; H, 5.18; N, 17.29.

Methyl 2,3-Di-*t*-butylcarbazate. A. Base-Catalyzed Preparation.—A solution of sodium methoxide (prepared from 0.23 g, 10 mg-atoms of sodium and 25 ml of methanol) and 1.00 g (5.88 mmol) of di-*t*-butyldiaziridinone was heated at reflux for 1 hr. After 40 min of reflux only a trace of the diaziridinone was detectable by infrared. Methanol was removed on a rotary evaporator until the volume was 10 ml and this was poured into 60 ml of water. The resulting mixture was extracted with four 20-ml portions of pentane and then the combined pentane extracts were washed with four 30-ml portions of water. The pentane solution was dried ($MgSO_4$) and evaporated to afford 0.979 g of clear oil (82%) approximately 98% pure by glpc at 135°. This oil was purified by glpc to give 0.640 g of methyl 2,3-di-*t*-butylcarbazate: n^{25}D 1.4291; ir (CCl_4) 1700 cm^{-1}; nmr (CCl_4) 1.03 (s, 9 H), 1.31 (s, 9 H), 3.69 (s, 3 H), 3.94 (1 H, broad).

Anal. Calcd for $C_{10}H_{22}N_2O_2$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.15; H, 10.78; N, 14.13.

B. Acid-Catalyzed Preparation.—A solution of 250 mg (1.47 mmol) of di-*t*-butyldiaziridinone in 25 ml of methanol (distilled from sodium methoxide) was heated at reflux under nitrogen for 2 hr. An infrared spectrum showed only slight decomposition of the diaziridinone. Concentrated sulfuric acid (5 mg) was added and, after 5 min at reflux, no diaziridinone remained (by infrared). The methanol was removed on a rotary evaporator and the residual clear oil was dissolved in 8 ml of pentane. The pentane solution was washed with three 4-ml portions of water and then evaporated leaving 200 mg (67%) of oil. This was purified by glpc at 135° to afford 118 mg of methyl 2,3-di-*t*-butylcarbazate.

Reaction of Di-*t*-butyldiaziridinone with Methanol.—Diaziridinone, 0.25 g (1.5 mmol), was dissolved in 20 ml of methanol. Infrared analysis indicated that the diaziridinone was consumed in 43 hr at room temperature. The excess methanol was removed under vacuum to leave a clear, colorless oil, 0.31 g (1.5 mmol, 100%), crude methyl 2,3-di-*t*-butylcarbazate (**8f**) by glpc (column E, 155°) with methanol as its only impurity. Distillation (25°, 0.02 mm) left only a 0.2-mg residue.

Reaction of Di-*t*-butyldiaziridinone (1a) with Isopropylamine.—Isopropylamine (Eastman), 1.04 g (17.6 mmol), and 3.00 g (17.6 mmol) of 1a were allowed to react for 96 hr at room temperature under dry nitrogen. Repeated trituration and recrystallization of the resulting liquid–solid mixture at −20°

with pentane (50 ml) afforded two fractions. The less soluble, high melting material, 584 mg (3.78 mmol, 43%) (mp 181–188°) was identified as 1,3-diisopropylurea by mp 189–191° (after recrystallization from methanol–benzene) (lit.[26] mp 192°), mmp 189–191°, and an ir spectrum identical with an authentic one. The low melting, more soluble fraction, 1.406 g (6.14 mmol, 35%), mp 93–95°, was subjected to repeated low temperature recrystallization from pentane: needles; mp 93–94°; ir (CCl_4) 3440 b, 2250 w, 1670 s, 1450 m, 1175 m, 1495 s, 1360, 1380 cm^{-1}; nmr (CCl_4) 0.94 (d, 6 H), J = 6.2 Hz), 0.95 (s, 9 H), 1.07 (s, 9 H), 3.88 (m, 1 H, J = 6.2 Hz). From this spectral evidence and the evidence presented below, the compound was assigned structure **10**, 1,2-di-*t*-butyl-4-isopropylsemicarbazide.

Anal. Calcd for $C_{12}H_{27}N_3O$: C, 62.84; H, 11.87; N, 18.32; mol wt, 229.3. Found: C, 63.10; H, 11.83; N, 18.54; mol wt, 237 ± 10 (vapor osmometer in benzene).

The pentane filtrates from above were subjected to glpc analysis at 138° on column E. The following components were identified: 2,2′-dimethyl-2,2′-azopropane (assayed 11.5%, 2.03 mmol), **1a**, and the thermal decomposition products of semicarbazide **10**. (Under the conditions of the analysis semicarbazide **10** produced two peaks (of intensity indicating high conversion) which were identified as 1,2-di-*t*-butylhydrazine and isopropyl isocyanate.) Further observations indicated the equilibrium of **10** with the isocyanate and hydrazine. Compound **10** exhibits a weak peak at 2250 cm^{-1} (in CCl_4 solution) characteristic of isopropyl isocyanate. The compound has a sharp odor (isocyanate) and a pure sample sublimes readily at room temperature with the sublimate being less pure than the original sample. When isopropylamine was used in excess in this experiment the yield of the urea was enhanced at the expense of the semicarbazide **10**; 3.87 g (22.7 mmol) of **1a** in 10.0 g (169 mmol) of isopropylamine for 43 hr gave 2.568 g (16.7 mmol, 73.5%) of the urea and 0.565 g (2.46 mmol, 10.8%) of semicarbazide **10**.

When 1-*t*-butyl-3-isopropylurea was subjected to the reaction conditions above (excess isopropylamine) for 43 hr, no reaction occurred; only starting urea was recovered, mp 203–205°.

Reaction of Di-*t*-butyldiaziridinone with Hydrazine.—A solution of 3.44 ml (3.00 g, 17.6 mmol) of **1a** and 6.70 ml (5.60 g, 176 mmol) of anhydrous hydrazine (Eastman, $n^{25}D$ 1.4672) in 80 ml of *t*-butyl alcohol (distilled from sodium) was allowed to stand at room temperature under a dry nitrogen atmosphere. A small amount of heat was given off at first and a crystalline precipitate appeared which after 12 hr was collected by filtration, washed, and dried to give 1.114 g. An additional 342 mg was obtained by evaporation of the alcohol–hydrazine filtrate. The combined precipitates, identified as carbohydrazide **13**, 1.456 g (92.5%), had mp 155–158° [mmp 153.5–156°, authentic sample (Aldrich) 153.5–156°] and an ir spectrum identical with an authentic one. Analysis by glpc (column A, 112°) indicated 71.5% (12.4 mmol) di-*t*-butylhydrazine in the original filtrate.

A solution of 3.05 g (17.6 mmol) of 1,3-di-*t*-butylurea, 6.70 ml (5.60 g, 176 mmol) of hydrazine, and 80 ml of *t*-butyl alcohol was allowed to stand for 12 hr at room temperature under nitrogen. No precipitate was observed. Evaporation of the solvent and dilution with water afforded a total of 3.04 g (100% recovery) of the urea, mp 237–239°, mmp 239–240°.

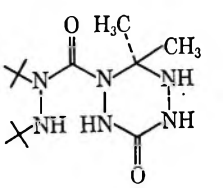
A solution of 3.44 ml (3.00 g, 17.6 mmol) of diaziridinone **1a**, 0.67 ml (0.56 g, 17.6 mmol) of hydrazine, and 20 ml of *t*-butyl alcohol after 12 hr at 25° afforded a precipitate, 364 mg (4.04 mmol), 46% of carbohydrazide **13**, mp 148° dec (recrystallization from methanol–water gave 199 mg, mp 152–155°, mmp 153.5–156°, and an ir identical with an authentic one.) Removal of the *t*-butyl alcohol from the filtrate under vacuum left a solid–liquid mixture, which was separated by filtration. The solid phase (after drying at 0.02 mm) appeared to be a ternary mixture of carbohydrazide **13** and two other components by tlc on silica gel. The liquid phase was largely unchanged **1a** (by ir) which also showed additional carbonyl absorption at 1650 cm^{-1}.

When 15 ml of ether was used as a solvent for the preceding experiment a precipitate of 1.45 g was obtained of which 510 mg was chromatographed over 20 g of neutral alumina (activity grade I). Elution with methanol afforded a nearly pure component (by tlc) which was obtained pure by recrystallization from $CHCl_3$, 200 mg (0.77 mmol represents 2.2 mmol, 25%) of a compound, mp 240° dec, R_f 0.7 on silica gel tlc with CH_3OH eluent, which is assigned as 1-(2,3-di-*t*-butylcarbazyl)carbohydrazide, **15**: ir ($CHCl_3$) 3385 (very broad and strong), 1670 (strong); 1450–1500 complex, 1385 w, 1360 cm^{-1} m; nmr (CD_3OD) 1.10 (s, 9 H), 1.38 (s, 9 H), 4.76 (broad, singlet, OH of CD_3OH representing the six NH's of **15**).

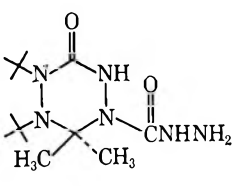
Anal. Calcd for $C_{10}H_{24}N_6O_2$: C, 46.13; H, 9.29; N, 32.28; mol wt, 260.34. Found: C, 45.86; H, 9.06; N, 32.31; mol wt, 240 (vapor osmometer, ethanol solvent).

A condensation product of carbohydrazide **15** and acetone was obtained from a solution of **15** in acetone as a white crystalline substance, mp 171°, assigned **19** (although the data do not exclude other structures such as **20**) by ir ($CHCl_3$) 3375 b, 1660 s, 1690 cm^{-1} sh; nmr ($CDCl_3$, all singlets) 1.15 (9 H), 1.42 (9 H), 1.73 (3 H), 1.99 (3 H), 3.8 (NH's). [This compound was not present (tlc) in the mixture before contact with acetone.]

Anal. Calcd for $C_{13}H_{28}N_6O_2$: C, 51.98; H, 9.39; N, 27.98; mol wt, 300.40. Found: C, 51.88; H, 9.32; N, 27.72; mol wt, 291 (osmotic in ethanol).



19



20

Reaction of Di-*t*-butyldiaziridinone with Phenylhydrazine.—A solution of **1a**, 1.72 ml (1.50 g, 8.8 mmol), and phenylhydrazine, 0.87 ml (0.95 g, 8.8 mmol; Eastman, mp 19–20°), in 35 ml of dry ether was prepared and rapidly stirred at 0° in an apparatus to measure gas evolution. Upon mixing a bright orange color developed. Gas evolved which was identified by gas–solid partition chromatography (column B, 140°) as nitrogen, 90%. In 31 min half of the nitrogen was evolved. Evolution was nearly linear with time for the first three-fourths of the reaction. After cessation of nitrogen evolution (4.5 hr) the liquid phase of the remaining solid–liquid mixture was found by glpc (column A, 56°) to contain 83.0% benzene. The solid phase was collected as fine, white needles by filtration and washed with 10 ml of ether. Evaporation of the ether afforded a solid–liquid mixture which when triturated with 10 ml of ether afforded additional white precipitate. Removal of the ether and repetition of the trituration procedure several times with 10-ml portions of pentane afforded a combined holding of 1.57 g (100%), 1,3-di-*t*-butylurea, identified by mp 241–242°, mmp 241–242°, and an ir spectrum identical with an authentic spectrum. The 230-mg residue proved to be a mixture of several components as demonstrated by tlc on silica gel (six were distinguishable using EtOAc). One of the components had the same color and R_f value as azobenzene. Separation of these components on neutral alumina was unsuccessful.

Very slow portionwise addition (over a 2-hr period) of an ether solution of phenylhydrazine to an ether solution of **1a** at 25° and addition in reverse order produced colored solutions which did not exhibit any fading with time.

Reaction of 2,4,6-Tri-*t*-butylphenol with Di-*t*-butyldiaziridinone.—2,4,6-Tri-*t*-butylphenol [Aldrich Chemical Co., mp 128–131° (lit. mp 131°) after recrystallization from isooctane], 0.52 g (2 mmol), and **1a**, 0.17 g (1 mmol), were dissolved in 7 ml of benzene (dried by azeotroping any water present), and sealed under vacuum after several degassings. The clear, colorless solution became pale blue after 5 min of heating at 100°; after 45 min an intense blue color was noted. After 20 hr at 100°, crystals had separated and the solution was a green color. The tube was opened and the crystals were isolated, washed, and dried: 14 mg (8.1%) of 1,3-di-*t*-butylurea identical with authentic material.

A solution of 17 mg (1 mmol) of **1a** and 52 mg (2 mmol) of 2,4,6-tri-*t*-butylphenol in 700 μl of benzene was degassed in a quartz tube and sealed under vacuum. After 2 days at room temperature an intense blue color was observed with the precipitation of fine needles. An intense esr spectrum was observed: a single sharp line, ascribed to the 2,4,6-tri-*t*-butylphenoxyl free radical, **14** (a single line at concentrations greater than 10^{-3} M).[27]

(26) A. W. Hofmann, *Ber.*, **15**, 756 (1882).

(27) E. Muller, K. Ley, K. Scheffler, and R. Mayer, *ibid.*, **91**, 2682 (1958).

Reaction of Di-*t*-butyldiazirdinone with Phenol.—A solution of 3.00 g (17.6 mmol) of 1a and 1.66 g (17.6 mmol) of phenol (mp 42–42.5°) in 40 ml of benzene was refluxed for 44 hr under nitrogen. White needles, 2.428 g (80%), were collected by filtration, washed, dried, and identified as 1,3-di-*t*-butylurea. Refluxing the filtrate for an additional 24 hr resulted in recovery of a polymeric material (rubbery, insoluble by swelled in benzene, nonmelting).

Reaction of Di-*t*-butyldiaziridinone with L-Ascorbic Acid.—A solution of 3.10 g (17.6 mmol) of L-ascorbic acid (mp 189–190.5°) and 3.00 g (17.6 mmol) of 1a in 12 ml of dimethylformamide became yellow and deposited needles after 1 min. After 12 hr at room temperature the needles were collected by filtration and washed with water. A total of 25 ml of water was added to the filtrate to precipitate additional crystals. After drying, the total amount, 1.403 g (45%), was identified as 1,3-di-*t*-butylurea, mp 241–242°, mmp 241–242°, and an ir spectrum identical with an authentic one. Attempts to convert any dehydroascorbic acid to a 2,4-dinitrophenylhydrazone derivative were unsuccessful.[28]

Reaction of Di-*t*-butyldiaziridinone with Benzohydrol.—A solution of 3.24 g (17.6 mmol) of benzhydrol (mp 66–67°) and 3.00 g (17.6 mmol) of 1a in 35 ml of benzene was refluxed under nitrogen for 10 days. After cooling, needles were collected, washed, and dried to give 437 mg of 1,3-di-*t*-butylurea, identified by mp 240–241.5°, mmp 240.5–242°, and an ir spectrum identical with an authentic one. The filtrate was composed of 1a, benzhydrol, and benzophenone by tlc analysis. Removal of the benzene and heating the residue for 48 hr at 100° afforded an oil–solid mixture of 1a, benzhydrol, and benzophenone. The latter was characterized as the semicarbazone derivative, 823 mg (3.42 mmol, 19.5% yield of benzophenone); recrystallization from benzene–isooctane gave mp 163–165.5°, mmp 162.5–165°, and authentic benzophenone semicarbazone mp 162–164.5° (lit.[29] mp 164–165°) with an ir spectrum identical with that of authentic semicarbazone.

Reaction of Di-*t*-butyldiaziridinone with Ethanethiol.—Ethanethiol (Eastman), 2.19 g (35.2 mmol), was distilled under a nitrogen atmosphere iuto a flask with 3.00 g (17.6 mmol) of 1a in 10 ml of pentane. The resulting solution was allowed to stand for 20 days at ambient temperature. After this time the contents of the flask were solid with a mat of long, fine needles, which were collected by filtration, washed with pentane, and dried: yield 1.00 g (33%), identified as 1,3-di-*t*-butylurea, by mp 236–238°, mmp 240–241°, and an ir spectrum identical with an authentic one. The pentane filtrate was subjected to glpc analysis at 130° (column E); only two components were observed: starting 1a, 54%, and diethyl disulfide, 34%.

Reaction of Di-*t*-butyldiaziridinone with Benzylthiol.—A solution of 1.15 ml (1.00 g, 5.88 mmol) of 1a and 1.38 ml (1.46 g, 11.76 mmol) of benzylthiol (Eastman) in 50 ml of benzene was refluxed for 24 hr under nitrogen which was sufficient to consume 30% 1a (determination by ir). The solution was reduced to about one-fourth the original volume and refluxed an additional 48 hr. Fine needles were filtered from the cooled solution. The filtrate, a pink solution, was reduced to an oil–solid mixture under vacuum, filtered, and the solid was washed with pentane. The combined solid fractions, 537 mg, were identified as 1,3-di-*t*-butylurea. The oil on fractional crystallization from methanol gave two crystalline fractions both with mp 68–155°, total weight 912 mg. Trituration of the solid with benzene, filtration, and evaporation of the benzene afforded 848 mg (59%) of plates identified as benzyl disulfide by mp 68.5–73°, mmp 68–74°, authentic sample (Eastman) mp 68–74° (lit.[30] mp 69–70°), and an ir spectrum identical with that of an authentic sample. Upon removal of solvent from the methanol filtrate a residue of 254 mg was obtained which when triturated with hexane gave 111 mg of the urea (mp 239–240°, mmp 240–241°). Total recovery of the urea was 648 mg (64%).

(28) J. Kenyon and N. Munro, *J. Chem. Soc.*, 158 (1948).
(29) W. Borshe and C. Merkwitz, *Ber.*, **37**, 3180 (1904).
(30) O. Hinsberg, *ibid.*, **41**, 632 (1908).

Reaction of 1-*t*-Butylhydroxylamine and D-*t*-butyldiaziridinone.—1-*t*-Butylhydroxylamine[31] was recrystallized from a dried (K_2CO_3) solution to give crystals, mp 58–60° (lit.[31] mp 64–65°). The 1-*t*-butylhydroxylamine, 1.56 g (17.6 mmol), and 3.00 g (17.6 mmol) of diazirdinone 1a were dissolved in 20 ml of benzene and refluxed 1.5 hr under a nitrogen atmosphere. The solution at this time was a very bright blue. Analysis by glpc (column A, 58°) revealed a single peak, 2-nitroso-2-methylpropane,[31] 41.3% (7.29 mmol). The remaining solution was filtered and the precipitate washed with benzene to give after drying 0.818 g of di-*t*-butylurea, identified by mp 239.5–240.5°, mmp 240.5–241.5°, and identity of ir spectrum. The filtrate and washings were reduced to an oil–solid mixture by evaporation under vacuum. An additional 43 mg of urea was recovered from the mixture by filtration (total yield, 861 mg, 4.99 mmol, 28.4%). The oil was distilled at 0.02 mm to give a fraction with bp 58–59°, 2.269 g (8.75 mmol, 49.4%), identified as (*t*-butylamino) 2,3-di-*t*-butylcarbazate, **17**, by ir (CCl_4) 3210 (sharp), 1695 s, 1475 m, 1390 m, 1370 m, 1305 s, 1200 cm^{-1} m; nmr (CCl_4, all singlets) 1.04 (9 H), 1.13 (9 H), 1.33 (9 H), 3.93 (broad, 1 H), 7.25 (broad, 1 H).

Anal. Calcd for $C_{13}H_{29}N_3O_2$: C, 60.19; H, 11.27; N, 16.20. Found: C, 60.17; H, 11.34; N, 16.20.

A small amount of diaziridinone 1a remained unchanged under these conditions—2.3% by ir analysis employing standard solutions.

Pyrolysis of (*t*-butylamino) 2,3-di-*t*-butylcarbazate, 17 [1-*t*-butyl-O-(2,3-di-*t*-butylcarbazyl)hydroxylamine], was carried out by heating a neat sample, 1.037 g (4.02 mmol), at 155–175° for 1 hr in a microdistillation apparatus with a gas volume measuring device. During the pyrolysis gas was evolved, pale yellow liquid distilled into the receiver, and white solid collected in the condenser. Only a trace of dark material remained in the pot at the end of the pyrolysis. The white solid was removed, washed with 25 ml of pentane, dried, and identified as 180 mg (1.03 mmol, 51.3% yield) of *t*-butylammonium *t*-butylcarbamate,[32] **18**, identical with an authentic sample prepared by treating *t*-butylamine with an excess of Dry Ice. Compound 18 decomposes (sealed tube) at 121–130°, mixture at 121–130°, and the authentic sample at 121–130°. The yellow liquid was identified as 2,2′-dimethyl-2,2′-azopropane by its display of a single major peak on glpc (column A, 58°) with a retention time and ir spectrum of a collected sample identical with authentic material. Quantitative determination gave an assay of 30.8% (1.24 mmol). The gas evolved was identified as 1.99 mmol (99%) of carbon dioxide by its precipitation of barium carbonate from a barium hydroxide solution. The low yields reported for the azo compound and **18** most likely reflect the mechanical difficulties in separation of the components. No blue color attributable to 2-nitroso-2-methylpropane was noted. Glpc analyses indicated a trace amount of di-*t*-butylhydrazine (identification by retention time only.) These results further establish structure **17** and exclude the alternative hydroxysemicarbazide structure for the product from reaction of 1-*t*-butylhydroxylamine with di-*t*-butyldiaziridinone.

Registry No.—1,3-Di-*t*-amylurea, 19656-71-4; 1-*t*-butyl-3-isopropylurea, 19656-72-5; 1,3-di-*t*-butyl-1-chlorourea, 19656-73-6; 1-chloro-1,3-di-*t*-octylurea, 19694-13-4; **1a**, 19656-74-7; **1b**, 19656-75-8; **1c**, 19656-76-9; **1d**, 19694-14-5; **1e**, 19656-84-9; 1,2-di-*t*-butyl-1-methylhydrazine, 19656-85-0; 1,2-di-*t*-butyl-1-formylhydrazine, 19656-86-1; **8b**, 19713-62-3; 1,2-di-*t*-butylhydrazine, 13952-69-7; 1-benzoyl-1,2-di-*t*-butylhydrazine, 19656-88-3; **8c**, 19656-89-4; **8e**, 19694-15-6; **8f**, 19694-16-7; **10**, 19656-90-7; **15**, 19694-17-8; **17**, 19694-18-9.

(31) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).
(32) M. B. Jensen, *Acta Chem. Scand.*, **11**, 499 (1957).

Diaziridinones. III. Reactions with Hydrazines. Isomerization of Diaziridinones to Aziridinecarboxamides by Hydrazine Catalysis[1]

FREDERICK D. GREENE, WILLIAM R. BERGMARK, AND J. GRADY PACIFICI

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received August 26, 1968

Diaziridinones, **1**, undergo oxidation–reduction and rearrangement reactions in the presence of substituted hydrazines. Reaction of di-*t*-butyldiaziridinone, **1a**, with 1,2-di-*t*-butylhydrazine, **2a**, affords 1,3-di-*t*-butylurea and azobis-2-methyl-2-propane (major products), 1-(*t*-butylcarbamyl)-2,2-dimethylaziridine, **3a** (*i.e.*, N-*t*-butyl-2,2-dimethylaziridinecarboxamide), in 20% yield, and a few per cent of di-*t*-butylcarbodiimide. In the reaction of di-*t*-butyldiaziridinone, **1a**, with 1,2-di-*t*-amylhydrazine, **2b**, and of di-*t*-amyldiaziridinone, **1b**, with 1,2-di-*t*-butylhydrazine, **2a**, azo product comes from hydrazo reactant, excluding an addition–fragmentation mechanism (Scheme I), and supporting a hydrogen-transfer mechanism for the reduction of diaziridinone to the urea. The rearrangement reaction, **1** → **3**, is favored by increasing lability of hydrogen β to nitrogen in the diaziridinone: **1b** and **2a** afford 1-(*t*-amylcarbamyl)-2,2,3-trimethylaziridine (77%) and the urea (7%); di-2-methyl-3-phenyl-2-propyl)diaziridinone, **1c**, and **2a** afford 99% 1-(2-methyl-3-phenyl-2-propylcarbamyl)-2,2-dimethyl-3-phenylaziridine, **3c**. N-*t*-Butyl-N′-(2-methyl-3-phenyl-2-propyl)diaziridinone and **2a** afford the corresponding urea (50%) and 1-(*t*-butylcarbamyl)-2,2-dimethyl-3-phenylaziridine, **3d** (50%). In the absence of the hydrazines, the diaziridinones are stable under the reaction conditions in the presence or absence of products, indicating that the hydrazines are true catalysts for the rearrangement reaction. Low hydrazine concentrations favor rearrangement reaction over reduction of diaziridinone. A decrease in either the size or the number of substituents on the hydrazine increases the rate of reaction and decreases the aziridinecarboxamide/urea ratio; even **1c** goes largely to the urea in the presence of 1,2-dimethylhydrazine. Tetramethylhydrazine is ineffective with **1a** and **1b**, but effects the isomerization of **1c** → **3c** (at a substantially slower rate than di-*t*-butylhydrazine). The results are discussed (eq 4–8) in terms of initial hydrogen atom transfer to oxygen of diaziridinone with N–N cleavage. Intermolecular transfer of a second hydrogen to this species leads to the urea; intramolecular hydrogen abstraction (6-center) followed by cyclization leads to an azacyclopropylcarbinyl radical, convertible into rearrangement product **3** by hydrogen atom transfer to an acceptor.

In the preceding paper[1a] the synthesis and a number of reactions of diaziridinones (**1**) were described. Reaction of diaziridinone **1a** with hydrazines was shown to depend markedly on the nature of the hydrazine. Reaction of **1a** with hydrazine afforded carbohydrazide *via* nucleophilic attack on carbonyl carbon (eq 1). Reaction of **1a** with phenylhydrazine afforded 1,3-di-*t*-butylurea, benzene, and nitrogen (eq 2). In this paper, the results of an examination of the reaction of diaziridinones with substituted hydrazines are described.

1a, R = $(CH_3)_3C$–
b, R = $CH_3CH_2C(CH_3)_2$–
c, R = $C_6H_5CH_2C(CH_3)_2$–

$$(CH_3)_3CNHNHC(CH_3)_3 + H_2NNHCONHNH_2 \quad (1)$$
2a

$$\mathbf{1a} \xrightarrow{C_6H_5NHNH_2} (CH_3)_3CNHCONHC(CH_3)_3 + C_6H_6 + N_2 \quad (2)$$

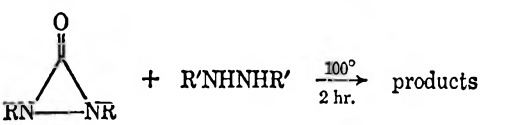
Results and Discussion

The over-all result of oxidation–reduction is a general reaction of hydrazines with **1a**. 1,1-Dimethylhydrazine, hydrazobenzene, and 1,2-di-*t*-butylhydrazine all effect the reduction of **1a** to the corresponding urea with concomitant oxidation of the hydrazine.

$$\mathbf{1a} + (CH_3)_3CNHNHC(CH_3)_3 \longrightarrow \underset{\mathbf{2a}}{} RNHCONHR + RN{=}NR \quad (3)$$

An early objective of this study was to ascertain whether the over-all oxidation–reduction sequence of eq 3 was initiated by nucleophilic attack on carbonyl carbon by the hydrazine (addition–fragmentation) or by a process involving hydrogen transfer from the hydrazine to the diaziridinone (Scheme I).

The distinction was sought in two "crossover" experiments: reaction of di-*t*-butyldiaziridinone with di-*t*-amylhydrazine and reaction of di-*t*-amyldiaziridinone with di-*t*-butylhydrazine.



1a, R = *t*-butyl **2a**, R′ = *t*-butyl
b, R = *t*-amyl **b**, R′ = *t*-amyl

Products	1a + 2b	1b + 2a
RNHCONHR	64	17
R′N=NR′	80[a]	30[a]
R′NHCONHR′	0	0
RN=NR	<0.4	<0.4

[a] The higher per cent of azo compound compared with urea is due to some air oxidation of reactant hydrazine.

In both experiments virtually all of the azo compound comes from the hydrazo reactant. These results exclude the addition–fragmentation sequence of Scheme I.

Although no "crossover" occurs, the yield of urea is considerably lower from **1b** than from **1a**. In large part, this reaction follows a different path; the major product is an isomer, **3b**, of diaziridinone **1b**. Examination of the di-*t*-butyldiaziridinone–di-*t*-butylhydrazine reaction also revealed the presence of a product, **3a**, isomeric with diaziridinone **1a**.

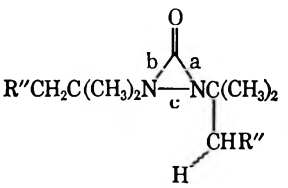
(1) (a) Part II: F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969). (b) Financial support from the National Science Foundation (Grant No. GP-5527) is gratefully acknowledged.

$1 + 2a \longrightarrow RNHCONHR + t\text{-BuN=N-}t\text{-Bu} + 3$

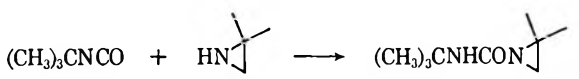
1a → 3a $C_9H_{18}N_2O$ Ir 3440, 1695 cm^{-1}
Nmr 1.28 (6 H, singlet), 1.38 (9 H, singlet), 2.07 (2 H, singlet), 5.03 (1 H, broad)

1b → 3b $C_{11}H_{22}N_2O$ Ir 3440, 1690 cm^{-1}
Nmr 0.85 (3 H, triplet, J = 7.5 Hz), 1.12 (3 H, doublet, J = 6 Hz), 1.16 (6 H, singlet), 1.23 (6 H, singlet), 1.58 (2 H, quartet, J = 7.5 Hz), 2.32 (1 H, quartet, J = 6 Hz), 4.82 (1 H, broad)

The isomerization is seen to involve the change of a C–H bond in the reactant to an N–H bond in the product with cleavage of bond a, b, or c of the diaziridinone, and formation of a new bond between the methylene carbon and one of the atoms of the N_2CO group. Of the large number of possible structures for

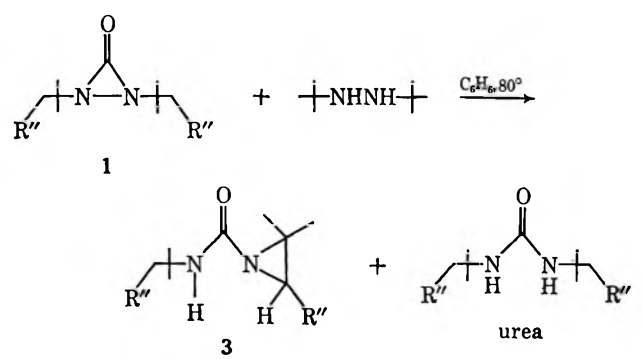


3, the physical data, coupled with the sensitivity of **3** to acid and to heat, were suggestive of the aziridinecarboxamide[2] structure, confirmed by synthesis from 2,2-dimethylaziridine and *t*-butyl isocyanate. From the reaction of **1b** with **2a** only one of the two possible aziridinecarboxamides was obtained, the one with a 2,2,3-trimethylaziridinyl moiety, **3b**.



The reaction of di-*t*-butyldiaziridinone with 1,2-di-*t*-butylhydrazine also affords di-*t*-butylcarbodiimide in 7% yield. Carbodiimides were not observed as products from the reactions of diaziridinones **1b** or **1c** with the hydrazines.

Consideration of the Diaziridinone Rearrangement Reaction. A. Effect of Structure of Diaziridinone.

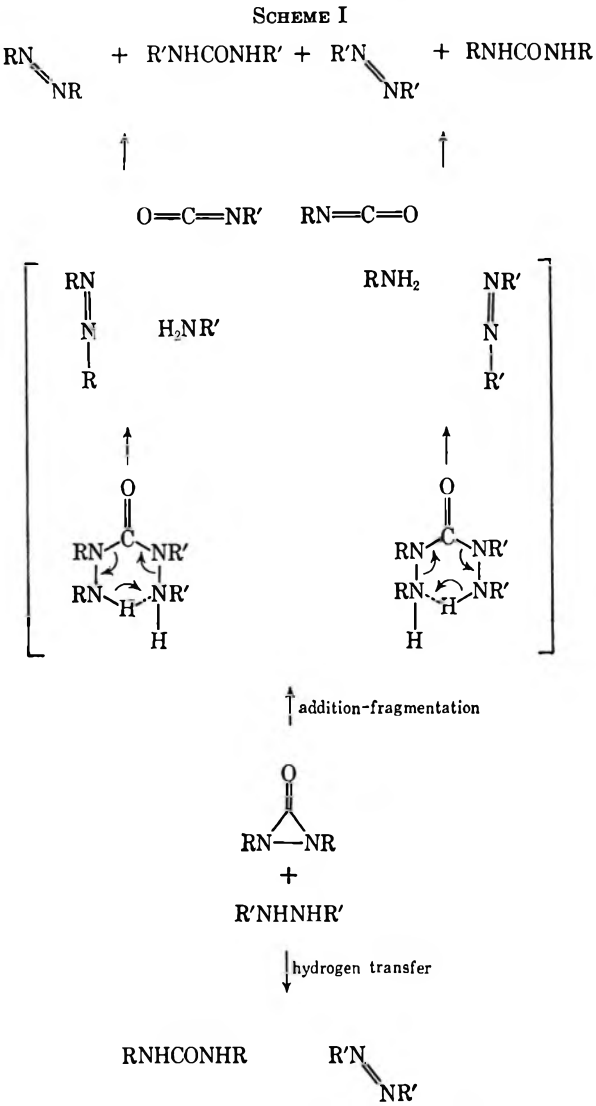


1	Yield, % 3	Urea	Time, hr
a, R″ = H	20	56	264
b, R″ = CH_3	77	7	18
c, R″ = C_6H_5	99	0	6

The change in character of C–H bonds that are β to the nitrogen from methyl to methylene to benzyl results in a marked increase in the rate of disappearance of diaziridinone and in an increase in the amount of reaction proceeding to the rearrangement product.

(2) H. W. Heine, *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962).

SCHEME I



B. Role of the Hydrazine.—In the absence of the hydrazine diaziridinones **1a–c** are stable in refluxing benzene over time periods severalfold longer than needed for the hydrazine–diaziridinone reactions. This stability of the diaziridinones is also observed when they are heated in the presence of the products of the hydrazine–diaziridinone reactions. Thus the isomerizations of **1a–c** to **3a–c** are not simple thermal reactions of the diaziridinones, but are reactions in which the hydrazines (or species derived therefrom) are true catalysts.

C. Effect of Concentration of the Hydrazine.

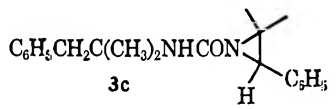
$$1a + 2a \xrightarrow[80°]{C_6H_6} 3a + t\text{-BuNHCONH-}t\text{-Bu}$$

Mole fraction 1a	Mole fraction 2a	Yield, % 3a	Yield, % *t*-Bu-NHCONH-*t*-Bu
0.08	0.92	0	85
0.1	0.08	20	56
0.1	0	No reaction	

The products and the product ratio are dependent on hydrazine, lower hydrazine concentrations favoring the isomerization reaction.

D. Effect of Structure of the Hydrazine.

1c + **2** ⟶



+ RNHCONHR

Hydrazine 2	Conditions	Yield, % 3c	Yield, % Substd urea
t-BuNHNH-*t*-Bu	6 hr, 80°	99	0
$CH_3NHNHCH_3$	20 min, 25°	3	80
$(CH_3)_2NNHCH_3$	1.5 hr, 80°	65	25

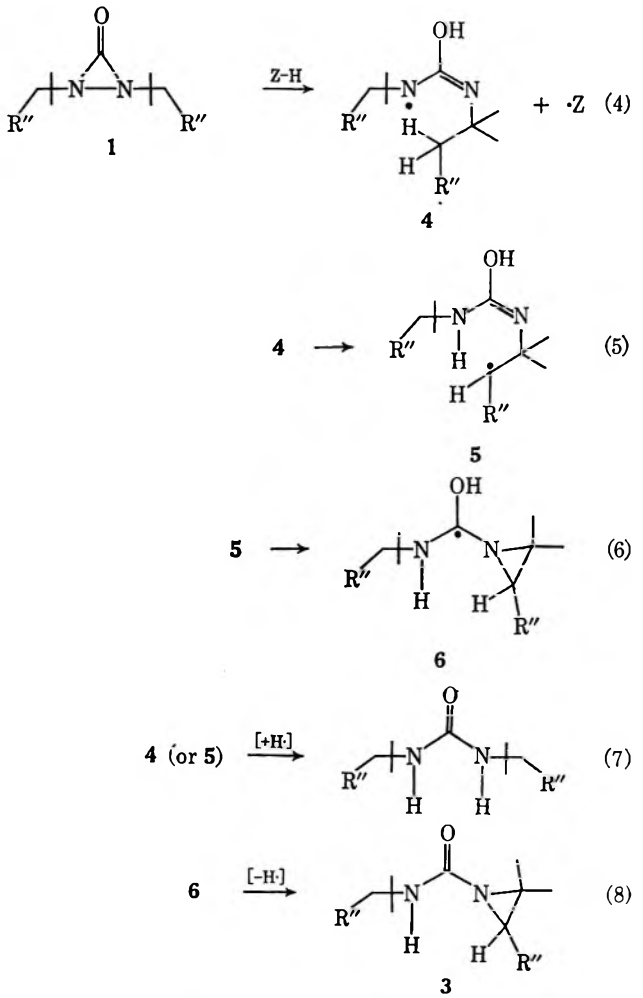
The rate of reaction and the competition between reduction and isomerization of diaziridinone are strongly dependent on the substituents on the hydrazine. Secondly, some urea is formed from the trimethylhydrazine indicating that the reduction reaction may proceed in successive single-hydrogen transfer steps.

Consideration of Hydrogen Transfer *vs.* Electron Transfer Mechanisms.—Conversion of diaziridinone into the corresponding urea obviously requires hydrogen transfers. Does the conversion of diaziridinone into the rearrangement product **3** *require* an N–H bond in the hydrazine or does it proceed by species such as a change-transfer complex between diaziridinone and the hydrazine, or by a radical anion chain mechanism? Di-*t*-butyldiaziridinone is unaffected by prolonged heating with tetramethylhydrazine although it reacts with 1,2-dimethylhydrazine at a moderate rate at room temperature and with 1,2-di-*t*-butylhydrazine with heating to give di-*t*-butylurea and **3a**. Di-*t*-amyldiaziridinone also is unaffected by prolonged heating with tetramethylhydrazine although it is largely converted into **3b** by warming with 1,2-di-*t*-butylhydrazine. Di(2-methyl-3-phenyl-2-propyl)-diaziridinone **1c** *is* converted into **3c** by heating with tetramethylhydrazine but at a rate that is 50-fold slower than with trimethylhydrazine.

If a charge-transfer complex[3] or full electron-transfer mechanism[3] were operative, one might expect a large increase in rate with increase in polarity of solvent.[4] The rough rate of disappearance of di-*t*-butyldiaziridinone in the presence of 1,2-di-*t*-butylhydrazine was severalfold faster in benzene than in *t*-butyl alcohol. The rate of disappearance of diaziridinone **1c** in the presence of tetramethylhydrazine was severalfold faster in *t*-butyl alcohol than in benzene, but little or no reaction took place between these reactants in acetonitrile (of the same *Z* value,[5] 71.3, as *t*-butyl alcohol).

These results do not provide support for mechanisms proceeding through charge-transfer complexes or radical anions for the rearrangement of diaziridinones **1a–c** to **3a–c** when the hydrazine possesses an N–H bond. The results do, however, point to a need for further study of the effect of electron donors on the diaziridinones.

Interpretation.—Of a large number of mechanisms we have considered, we favor the sequence outlined in eq 4–8: (a) the intramolecular hydrogen abstraction is depicted by nitrogen rather than by oxygen;[6–8] (b) the intramolecular hydrogen abstraction is *via* a six-atom transition state for which many examples are known,[9] and the selectivity in this abstraction is the expected one of benzyl C–H > methylene > methyl;[10] (c) the carbon radical formed by the intramolecular hydrogen abstraction is presented with only one suitable cyclization opportunity, affording an azacyclopropylcarbinyl radical,[11] **6**. The reader may verify for himself that initial hydrogen transfer to nitrogen requires more complicated mechanisms involving intramolecular abstraction by oxygen and/or hydrogen tautomerizations prior to ring closure.



A further point of interest concerns the reaction of the unsymmetrical diaziridinone, 1-*t*-butyl-2-(2-methyl-3-phenyl-2-propyl)diaziridinone, **1d**, with 1,2-di-*t*-butylhydrazine. This reaction affords only one of the two

(3) E. M. Kosower in "Progress in Physical Organic Chemistry," Vol. 3, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, New York, N. Y., 1965, p 81.

(4) E. M. Kosower and M. Mohammad, *J. Amer. Chem. Soc.*, **90**, 3271 (1968).

(5) E. M. Kosower, *J. Chim. Phys.*, **61**, 230 (1964).

(6) Amide radical intramolecular hydrogen abstractions are usually formulated this way (see ref 7), and a theoretical discussion on this point has been presented (ref 8). Experimental evidence on abstraction of hydrogen by N *vs.* O in amide radicals is slender, however.

(7) See R. S. Neale, N. L. Marcus, and R. G. Schepers, *J. Amer. Chem. Soc.*, **88**, 3051 (1966), and references cited therein.

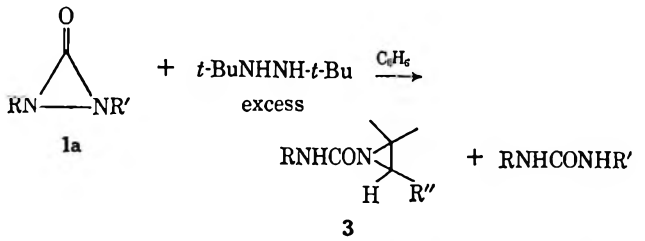
(8) E. Hedaya, R. L. Hinman, V. Schomaker, S. Theodoropulos, and L. M. Kyle, *ibid.*, **89**, 4875 (1967).

(9) See M. Akhtar in "Advances in Photochemistry," Vol. 2, W. A. Noyes, Jr., G. S. Hammond, and J. N. Pitts, Jr., Ed., Interscience Publishers, New York, N. Y., 1964.

(10) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, Chapter 12.

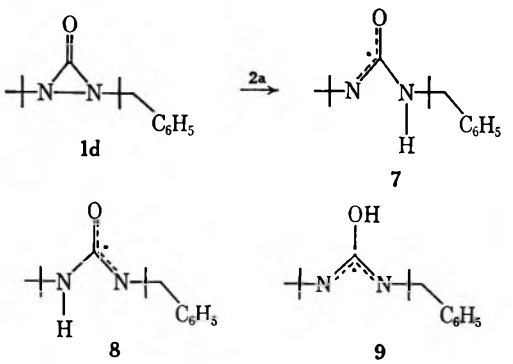
(11) For information on cyclopropylcarbinyl radicals, see L. K. Montgomery and J. W. Matt, *J. Amer. Chem. Soc.* **89**, 6556 (1967), and references cited therein.

possible rearrangement products *and an equal amount of the urea.* At first thought, these findings might

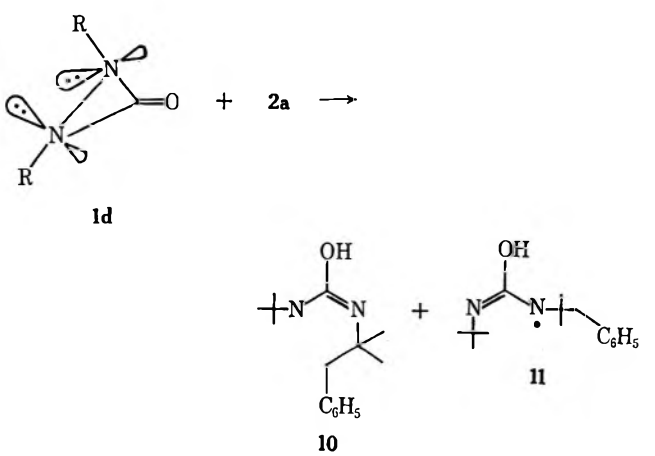


	Yield, % 3 (R″)	Urea
1a, R = R′ = *t*-butyl	~0 (H)	~90
1d, R = *t*-butyl R′ = $C_6H_5CH_2C(CH_3)_2$-	~50 (C_6H_5)	~50
1c, R = R′ = $C_6H_5CH_2C(CH_3)_2$-	~99 (C_6H_5)	~0

be considered to provide evidence for initial transfer of hydrogen from the hydrazine to nitrogen of the diaziridinone forming **7** and **8** in equal amounts, rather than to oxygen forming **9**, on the grounds that it is easier to rationalize the conversion of **8** into the rearrangement product **3d** and **7** into the urea than to account for the formation of **3d** and the urea *in equal amounts* from **9**.

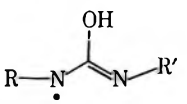


However, we believe that these findings are, indeed, more simply explained by initial transfer of hydrogen to oxygen. The physical evidence indicates a ground state for diaziridinones in which the substituents on the nitrogen atoms are in a *trans* orientation.[1a] Consider the transfer of hydrogen to diaziridinone with resultant disrotatory ring opening[12] to give **10** and **11**.



(12) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

These species are shown with the odd electron in a localized orbital with the understanding that the lone pair on the nitrogen which has the odd electron is in a p orbital conjugated with the adjacent carbon–nitrogen double bond.[8] Alternatively, the lone pair might be localized and the odd electron delocalized. The following conclusions are not dependent on a choice between these alternate representations of the radicals. The formation of the urea from **11** (in 50% yield based on **1d**) and the formation of the rearrangement product **3d** from **10** (in 50% yield based on **1d**) are then the expected results (a) if **10** and **11** are formed in approximately equal amounts from reaction of **1d** with **2a** and (b) if the rates of intramolecular hydrogen abstraction (leading to rearrangement product from **10**) and intermolecular hydrogen abstraction (leading to the urea from **11**) are faster than the rates of interconversion (by rotation around the C–N bonds or by nitrogen inversion) of **10**, **11**, and **12**.



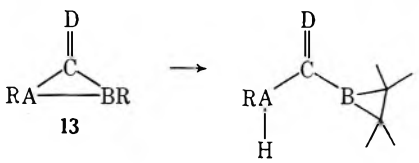
12

Many questions remain, such as the degree of chain character in the isomerization reaction (eq 9 *vs.* eq 10).

$$6 + \text{RNHNR} \longrightarrow 3 + \text{RNHNHR} \quad (9)$$

$$6 + 1 \longrightarrow 3 + 4 \quad (10)$$

It will also be of interest to ascertain whether this type of isomerism occurs in other three-ring systems. Efforts to effect this type of change with *trans*-di-*t*-butylcyclopropanone[13] have been unsuccessful. Bond energy considerations are suggestive of decreasing driving force for the isomerization reaction as one goes from diaziridinones (**13**, A = B = N; C = C; D = O) to aziridinones (**13**, A = N; B = C = C; D = O) to cyclopropanones (**13**, A = B = C = C; D = O).



Experimental Section

All melting points of 1,3-di-*t*-butylurea were taken in tubes sealed under vacuum. Infrared spectra are reported in cm^{-1} with the following notations: vs, very strong intensity; s, strong; m, medium; w, weak; b, broad; sh, shoulder; and sp, sharp. Nuclear magnetic resonance spectra were determined at 60 Mc; signals are reported in parts per million (ppm) downfield from tetramethylsilane. Gas–liquid partition chromatographic analyses (glpc) were performed with helium carrier gas and thermal conductivity detectors with the following columns: column A [a 6 ft × 0.25 in. aluminum tube packed with 20% (w/w) silicone oil "SE- 0" on a 60/80 mesh Chromosorb W diatomite support employing a flow rate of 65 cc/min]; column C [a 6 ft × 0.25 in. aluminum tube packed with silicone oil DC 200 on a 80/100 mesh Chromosorb P diatomite washed to a pH 8]. All identifications (unless otherwise noted) of glpc components were made by the identity with an authentic sample of both retention time and ir spectrum of a collected sample. All quantitative analyses were made by the internal standardization method unless otherwise noted. Assessment of error

(13) J. F. Pazos and F. D. Greene, *J. Amer. Chem. Soc.*, **89**, 1030 (1967).

was obtained in several of the analytical series by matching two or more standard solutions against each other. Error was found to be ±2%. (In one series the results are known to only ±10% as reported in the text.)

1-*t*-Butyl-3-(2-methyl-3-phenyl-2-propyl)urea was prepared by reaction of 2-methyl-3-phenyl-2-propylamine in hexane with *t*-butyl isocyanate. After standing overnight, the hexane was removed and the white solid was recrystallized from hexane or ethanol–water: yield 39.0 g (91%); mp 164.5–165.0°; nmr ($CDCl_3$) δ 1.29 (s, 6 H), 1.37 (s, 9 H), 3.08 (s, 2 H), 4.0 (broad, 2 H), and 7.29 (s, 5 H); ir ($CHCl_3$) 3440 (b, NH), 2970, 1678 (s, urea), and 1515 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.56; H, 10.01; N, 11.07.

1-*t*-Butyl-2-(2-methyl-3-phenyl-2-propyl)diaziridinone, 1d, was prepared in 72% yield by the method described previously:[1a] bp 86–92° (0.02 mm); $n^{24.8}D$ 1.4480; nmr ($CDCl_3$) δ 1.12 (s, 6 H), 1.21 (s, 9 H), 2.86 (s, 2 H), and 7.22 (s, 5 H); ir ($CHCl_3$) 3075 (w, Ph), 2945, 2985 (s), 1870 (s, C=O) and 1600 cm^{-1} (w, Ph).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.12; H, 9.00; N, 11.37. Found: C, 72.85; H, 8.95; N, 11.32.

Diaziridinones 1a–c were described in part II.[1a]

1,2-Di-*t*-amylhydrazine was prepared by adding 9.90 g (50 mmol) of diaziridinone **1b** slowly under a nitrogen atmosphere to 100 ml of 15% aqueous HCl with rapid stirring. The solution was stirred an additional 5 min after the turbidity and evolution of gas ceased. The solution was cautiously made basic with 40% aqueous NaOH solution and extracted under nitrogen with a 300-ml portion of pentane. The pentane extract was dried (nitrogen atmosphere) by passing through a short column of anhydrous K_2CO_3. Removal of the pentane afforded 7.02 g (82%) of crude hydrazine which was purified for use by preparative glpc (column E, 155°). The purified hydrazine had ir (CCl_4) 3225 (b), 1455 (m), 1375 (m), 1175 cm^{-1}(m); nmr (CCl_4) 0.95 (s, 6 H, J = 7.5 Hz), 0.98 (s, 12 H), 1.39 (quartet, 4 H, J = 7.5 Hz), 2.71 (broad singlet, 2 H); $n^{22.5}D$ 1.4316.

Anal. Calcd for $C_{10}H_{24}N_2$: C, 69.70; H, 14.04; N, 16.26. Found: C, 70.03; H, 13.84; N, 16.33.

2,2′-Dimethyl-2,2′-azobutane.—A mixture of 1,2-di-*t*-amylhydrazine (1.00 g, 5.8 mmol), yellow mercuric oxide (10.00 g, 46.2 mmol), and 10 ml of water was shaken vigorously in a stoppered flask for 1 hr and allowed to stand overnight. The mixture was then extracted with three 15-ml portions of pentane which were combined and dried (K_2CO_3). Removal of the pentane afforded 0.838 g (84%) of crude azo compound which showed only pentane as an impurity in glpc (column E, 155°) and after purification by preparative glpc had ir (CCl_4) 1465, 1360, 1380 cm^{-1}; nmr (CCl_4) 0.81 (triplet, 6 H, J = 7.5 Hz), 1.10 (s, 12 H), 1.68 (quartet, 4 H, J = 7.5 Hz); $n^{23.0}D$ 1.4175.

Anal. Calcd for $C_{10}H_{22}N_2$: C, 70.52; H, 13.02; N, 16.45. Found: C, 70.76; H, 12.96; N, 16.55.

The oxidation did not occur when a dry pentane solvent was used with no aqueous phase.

1-(*t*-Butylcarbamyl)-2,2-dimethylaziridine (N-*t*-butyl-2,2-dimethyl-1-aziridinecarboxamide), 3a, was prepared by adding a solution of 3.97 g (40.0 mmol) of *t*-butyl isocyanate in 60 ml of pentane over a 30-min period to a stirred solution of 2.90 g (40.8 mmol) of 2,2-dimethylaziridine[14] in pentane over nitrogen in a dry apparatus at room temperature. After an additional 30 min of stirring, the solution was evaporated to dryness under vacuum affording 5.976 g (35.1 mmol, 88%) of crude aziridinecarboxamide **3a**, mp 67–74° (ir not distinguishable from pure **3a**), which was fractionally sublimed at 50–70° (0.02 mm). Five recrystallizations from pentane of the first sublimed fraction gave pure **3a** with constant mp 77.5–78.5°; ir (CCl_4) 3440 (sp), 1695 (s), 1495 (s), 1455, 1390, 1380, 1370, 1340 cm^{-1}; nmr (CCl_4, all singlets) 1.28 (6 H), 1.38 (9 H), 2.07 (2 H), 5.03 (NH).

Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.65; N, 16.46. Found: C, 63.26; H, 10.64; N, 16.46.

Elution of 200 mg of **3a** over 10 g of silica gel with 60 ml of ethyl acetate afforded 166 mg of material, mp 123–170°. Similarly glpc of **3a** (column A) gave only high-melting mixtures from the exit port. The use of adsorbants (Norit) and ethyl acetate, methylene chloride, and methanol as recrystallization solvents were not effective in purification of **3a**. The compound is decomposed by heating and by the action of acids (probably converted into an oxazoline).[2]

N-(2-Methyl-3-phenyl-2-propyl)-2,2-dimethyl-3-phenyl-1-aziridinecarboxamide, 3c, was prepared by the above method in 86% yield from 2,2-dimethyl-3-phenylaziridine[15] and 2-methyl-3-phenyl-2-propyl isocyanate:[16] mp of **3c**, 118–119°; nmr ($CDCl_3$) δ 0.87 (s, 3 H), 1.21 (s, 3 H), 1.24 (s, 3 H), 1.31 (s, 3 H), 2.74 (d, 1 H, J = 13 Hz), 3.13 (d, 1 H, J = 13 Hz), 3.30 (s, 1 H), 4.70 (broad singlet, 1 H), and 7.06, 7.07 (d, 10 H); ir (CCl_4) 3440 (s), 3020 (m), 1690 (s), and 1600 cm^{-1} (w). The magnetic nonequivalence of the methylene hydrogens and the adjacent methyls of the $C_6H_5CH_2C(CH_3)_2$– group is of special interest in view of their separation by 5 (and 4) bonds from the chiral center in the aziridine moiety.

Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.44; H, 8.26; N, 8.73.

N-*t*-Butyl-2,2-dimethyl-3-phenyl-1-aziridinecarboxamide, 3d, was prepared from the aziridine[14] and *t*-butyl isocyanate in hexane: mp 174–175° (from benzene); nmr ($CDCl_3$) δ 0.97 (s, 3 H) 1.35 (s, 12 H), 3.50 (s, 1 H), 5.0 (broad, 1 H), and 7.27 (s, 5 H); ir ($CHCl_3$), 3420 (NH), 1680 (amide), and 2950 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.15; H, 9.25; N, 11.42.

Reaction of 1,2-Di-*t*-butylhydrazine, 2a, with Di-*t*-butyldiaziridinone, 1a. A. In Benzene.—A solution of 2.292 g (13.46 mmole) of **1a**, 1.511 g (10.48 mmol) of **2a**, and 1.695 g of bromobenzene (internal standard) in 10 ml of oxygen-free benzene was refluxed for 11.0 days under a dry nitrogen atmosphere. The course of the reaction was followed by glpc (column A, 112°) and ir. The products, 2,2′-dimethyl-2,2′-azopropane and di-*t*-butylcarbodiimide,[17] were identified and isolated from glpc [the carbodiimide was also indicated by ir (2100-cm^{-1} doublet) in the reaction solution]. Upon cooling, the reaction mixture contained a mat of fine, white needles which were collected by filtration and washed with a small amount of pentane, dried at 0.02 mm, and identified as 1.203 g (6.98 mmol, 52%) of 1,3-di-*t*-butylurea by mp 236–237°, mmp 236.5–237°, and an ir spectrum identical with that of an authentic sample. The combined filtrate and washings were evaporated to dryness (0.02 mm, 12 hr) affording white crystals, 534 mg, mp 72–105°, purified by combinations of fractional sublimation and fractional recrystallization from pentane to afford 153 mg of 1-(*t*-butylcarbamyl)-2,2-dimethylaziridine, **3a**, identified by mp 79–81°, mmp 79–81°; ir, nmr spectra, and chromatographic behavior were all identical with synthetic sample data. The crude material was assayed by a glpc method using column A (110°), indicating 19% of **3a** and an additional 4% of the urea. Under the conditions chosen the aziridinecarboxamide **3a** gives a single peak of reproducible retention time even though collection of the eluted peak affords no **3a** but only high-melting material. Furthermore, the response factor (relative to the urea for example) is abnormally low suggesting that this peak does not represent all the injected material. The use of these glpc conditions as a method for quantitative analysis for both **3a** and the urea was found to be valid, however, by the cross-checkings of standard solutions. Error of the measurements was found to be ±10% of the actual value. Analysis of the original reaction solution by this method gave the following results. After 1 day, 58% of **1a** and 55% of **2a** had been consumed; 49% 2,2′-dimethyl-2,2′-azopropane had formed. After 7 days, 90% of **1a** and 83% of **2a** had been consumed; 87% azo compound and 7% di-*t*-butylcarbodiimide had formed. After 11 days, 99% of **1a** and 89% of **2a** had been consumed; 94% azo compound and 7.5% carbodiimide had formed. The yield (see above) of di-*t*-butylurea was 56%, of 1-*t*-butylcarbamyl-2,2-dimethylaziridine **3a** was 20%. The ir of the product mixture had weak absorption at 2250 cm^{-1} (isocyanate). A solution of **1a** (0.8 M) and **2a** (0.092 M) in benzene gave the urea (11% based on 1a, 92% based on **2a**) and **3a** (5.6% based on 1a). A solution of **1a** (0.5 mmol) and **2a** (5.5 mmol) was heated (sealed tube) without added solvent for 45 hr at 86°, giving the urea in 85% yield and no **3a**.

B. In *t*-Butyl Alcohol.—A solution of 2.545 g (14.9 mmol) of **1a** and 1.529 g (10.6 mmol) of **2a** in 10.0 ml of *t*-butyl alcohol (distilled from sodium and deoxygenated with dry nitrogen)

(14) K. C. Campbell, A. H. Sommers, and B. K. Campbell, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 148.

(15) S. J. Brois, *J. Org. Chem.*, **27**, 3532 (1962).

(16) British Patent 613,111 (Nov 23, 1948); *Chem. Abstr.*, **43**, 5800*h* (1949).

(17) E. Schmidt and M. Seefelder, *Ann.*, **571**, 83 (1951).

was refluxed for a total of 25 hr under nitrogen: diaziridinone (determined by ir) remaining after 3.5 hr, 42%; 14.5 hr, 15%; and 20 hr, 11%. Analysis for products by the above methods gave 60% di-*t*-butylurea and 12% **3a**.

Aliquots of a solution of 17.8 mg (0.105 mmol) of **1a** and 79.0 mg (0.547 mmol) of **2a** in 1.00 ml of benzene (dried over Na, distilled on a Teflon spinning-band column and deoxygenated with nitrogen) were sealed in capillary tubes and heated at 86.0 ± 0.01°. The tubes were opened periodically and the diaziridinone concentration was measured by ir. A solution of 18.6 mg (0.109 mmol) of **1a** and 78.0 mg (0.540 mmol) of **2a** in 1.00 ml of *t*-butyl alcohol (distilled from Na) was also examined in the same way. Time for 20% reaction: benzene, 14 hr; *t*-butyl alcohol, 70 hr. Time for 40% reaction: benzene, 23 hr; *t*-butyl alcohol, 120 hr.

Reaction of Diaziridinone 1a with 1,2-Dimethylhydrazine.—A solution of 737 mg (12.3 mmol) of 1,2-dimethylhydrazine[18] and 2.41 ml (2.10 g, 12.3 mmol) of **1a** in 60 ml of fresh, dry ether was refluxed for 36 hr under nitrogen. During this time fine, white crystals deposited. Use of an apparatus to measure gas evolution indicated that none was employed. A single compound was found in the liquid phase on glpc analysis (column C, 25°), azomethane, 76.5%. [The standard azomethane solution for quantitative determination was prepared by oxidizing a known amount of 1,2-dimethylhydrazine with mercuric oxide in ether and 2,3-dimethylbutane (internal standard) solution.] Analysis for products indicated 80% di-*t*-butylurea, no **3a**, and a small amount of an unidentified material with ir 1655 cm^{-1}.

Reaction of Di-*t*-butyldiaziridinone (1a) with Hydrazobenzene.—A solution of 2.15 g (11.7 mmol) of hydrazobenzene and 2.00 g (11.7 mmol) of **1a** in 50 ml of benzene was refluxed under nitrogen for 115 hr, monitoring by ir. The resulting mixture was cooled and filtered; the collected needles were washed and dried to yield 1.547 g of 1,3-di-*t*-butylurea. Analysis of the filtrate by uv at λ 319 indicated 89% azobenzene. Work-up of the filtrate afforded 112 mg of the urea (total yield of urea, 1.66 g, 78%) and 1.55 g (73% yield) of azobenzene, isolated by chromatography on alumina, mp 67–68°, mmp 67–68°.

"Crossover Experiments." A. Reaction of 1,2-Di-*t*-amylhydrazine, 2b, with Di-*t*-butyldiaziridinone, 1a.—Hydrazine **2b** (purified by preparative glpc), 148 mg (0.851 mmol), and 134 mg (0.786 mmol) of diaziridinone **1a** (along with a bromobenzene internal standard) were sealed in a tube and allowed to stand 21 days at room temperature (heating 12 hr at 100° gives the same results) to produce a mass of fine, white crystals with interstitial liquid phase. The liquid phase was examined by glpc (column A, 112°) and found to contain 2,2′-dimethyl-2,2′-azobutane and starting hydrazine **2b**. Recovery of the **2b** as such or as the azo compound was 98%. A certain amount of the hydrazine would air oxidize on handling the reaction mixtures which was accounted for by blanks. A minor component, 2,2′-dimethyl-2,2′-azopropane, was observed in a 0.34% yield. (There was not a sufficient amount of it for an ir spectrum; its identification is based on retention time alone.) The solid fraction from the reaction was collected by centrifugal filtration, washed five times with 250-μl portions of pentane, and dried 12 hr *in vacuo* to give white crystals [84 mg (64% yield), identified as 1,3-di-*t*-butylurea by mp 237.4–238°, mmp 238.5–239.5° (mmp with **3b**, 222–224.5°)], and an ir spectrum identical with that of authentic 1,3-di-*t*-butylurea (but different from 1,3-di-*t*-amylurea). An ir spectrum of the liquid phase showed a very small amount (1–2%) of starting **1a**.

B. Reaction of 1,2-Di-*t*-butylhydrazine, 2a, with Di-*t*-amyldiaziridinone, 1b.—A solution of 1.516 g (10.50 mmol) of **2a** and 2.105 g (10.60 mmol) of **1b** in 10 ml of benzene was refluxed under a nitrogen atmosphere for 18 hr. Analysis by ir showed no diaziridinone remaining after this time. Bromobenzene was added and the solution analyzed by glpc (column A, 112°). A 33% yield of 2,2′-dimethyl-2,2′-azopropane was found. Azo-hydrazine recovery (mmoles of 2,2′-dimethyl-2,2′-azopropane found + mmoles of **2a** remaining/mmoles of starting **2a**) was 102%. The residual solid obtained after removal of volatile components under vacuum was separated by fractional recrystallization from pentane into two components, 135 mg (6.8%) of di-*t*-amylurea,[1a] mp 209–213°, and 1.61 g (76.5%) of a substance which after purification by several sublimations and recrystallizations from pentane was identified as 1-(*t*-amylcarbamyl)-2,2,3-trimethylaziridine, **3b**: mp 90–91°; nmr (see Results); ir (CCl_4) 3440 (sp), 1690 (s), 1495 (s), 1385 (sh), 1380 (m), 1365 (w), 1255 cm^{-1} (m); mol wt (osmotic, benzene), 195 (calcd 198).

Anal. Calcd for $C_{11}H_{22}N_2O$: C, 66.62; N, 11.15; N, 14.13. Found: C, 66.34; H, 11.08; N, 14.13.

Control experiments with hydrazine **2a** alone in benzene indicated some oxidation to azo compound.

When this reaction was run under conditions parallel to those of the reaction of hydrazine **2b** with diaziridinone **1a**, the results were essentially the same as those described above with the following exceptions: the experiment at room temperature for 20 days (**2a**, 1.00 mmol; **1b**, 0.933 mmol) resulted in a 17% yield of di-*t*-amylurea and 68% aziridinecarboxamide **3b**. A minor component, 2,2′-dimethyl-2,2′-azobutane (0.4%), was also observed (identification based on retention time only).

When 150 mg of **1b** was heated for 12 hr at 100° in a sealed tube, very little decomposition was observed; a very small 1690-cm^{-1} band appeared and a slight yellow color was noted. No significant change in diaziridinone concentration was observed from the absorbance of the carbonyl group in the ir.

Reaction of Di(2-methyl-3-phenyl-2-propyl)diaziridinone, 1c, with 1,2-Di-*t*-butylhydrazine, 2a.—A solution of 666 mg (2.065 mmol) of **1c** and 404 mg (2.80 mmol) of **2a** in 10 ml of benzene was refluxed for 18 hr under a positive pressure of nitrogen. Analysis by ir indicated no diaziridinone remained. Removal of the volatile components left a residue which when triturated with pentane afforded a total of 623 mg (94% yield) of a single component (tlc), mp 107–110°. Recrystallization from isooctane afforded pure 1-[(2-methyl-3-phenyl-2-propyl)carbamyl]-2,2-dimethyl-3-phenylaziridine, **3c**, mp 117.5–118.5°, identical with the synthetic sample. Diaziridinone **1c** under these reaction conditions undergoes no change when **2a** is absent.

A solution of 293 mg (0.91 mmol) of **1c** and 41 mg (0.28 mmol) of **2a** in 5 ml of oxygen-free benzene was degassed and heated in a sealed tube at 80° for 6 hr. The volatile components were removed under vacuum (reaching 0.02 mm for 12 hr) to leave a residue of 290 mg of **3c** (0.90 mmol, 99%), mp 115–116°, which when recrystallized from isooctane gave 276 mg, mp 116.5–117.5°. The rate of this reaction was not retarded by the use of rigorously purified benzene (distilled on a Teflon spinning-band column).

Reaction of Diaziridinone 1c with 1,2-Dimethylhydrazine.—A solution of 800 mg (2.48 mmol) of **1c** and 0.207 mg (180 mg, 3.00 mmol) of 1,2-dimethylhydrazine[18] in 10 ml of oxygen-free benzene over a nitrogen atmosphere at room temperature became warm, was diaziridinone free within 20 min (ir), and deposited fine, white crystals. The crystals were collected by filtration and the filtrate was reduced to dryness under vacuum. Trituration with a total of 35 ml of isooctane afforded an insoluble fraction which was combined with the crystalline precipitate and identified as 633 mg (1.95 mmol, 79%) of di(2-methyl-3-phenyl-2-propyl)urea by mp 179–180.5°, mmp 179–181° (authentic sample mmp 179.5–182°),[1a] and an ir spectrum identical with an authentic one. A total of 20 mg (0.062 mmol, 2.5%) of a substance was crystallized from a pentane solution of the soluble fraction; it was identified as aziridinecarboxamide **3c**, ir spectrum virtually identical with that of authentic **3c**.

Reaction of Diaziridinone 1c with Trimethylhydrazine.—A solution of 324 mg (1.00 mmol) of **1c** and 358 mg (4.83 mmol) of trimethylhydrazine[19] in 10 ml of purified and deoxygenated benzene was allowed to stand 22 hr at room temperature with little reaction occurring (ir). The solution was then refluxed for 1.5 hr after which no diaziridinone remained. The resulting pale yellow solution was evaporated to dryness affording a white solid. The solid afforded a soluble and an insoluble fraction upon trituration with 25 ml of hot isooctane. The former, 203 mg (0.63 mmol, 63%), was identified as aziridinecarboxamide **3c** by mp 108.5–112.5°, mmp 110–115.5° (when recrystallized from pentane, mp 116.5–117.5°, mmp 117–118°), and an ir spectrum identical with an authentic one. The latter fraction, 88 mg (0.27 mmol, 27%), was identified as di(2-methyl-3-phenyl-2-propyl)urea, mp 175.5–178.5°, mmp 178.5–180.5°, and an ir spectrum identical with an authentic one.[1a]

Reaction of Diaziridinone 1c with Tetramethylhydrazine.—A solution of 342 mg (1.095 mmol) of **1c** and 115 μl (88 mg, 1.00

(18) Liberated from the hydrochloride (Aldrich Chemical Co.) and purified by the method of H. H. Halt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 211.

(19) R. T. Beltrami and E. R. Bissell, *J. Amer. Chem. Soc.*, **78**, 2467 (1956).

mmol) of tetramethylhydrazine[18] in 5 ml of benzene was sealed in tubes under vacuum and heated at 80 ± 3° for 50 hr. The course of the reaction was followed by ir. The resulting solution was evaporated under vacuum to an oil which crystallized. The crystals, 355 mg (1.10 mmol, quantitative), were identified as aziridinecarboxamide **3c** by mp 110–113°, mmp 113–116°, and an ir spectrum identical with that of an authentic sample. Diaziridinone **1c** was totally unchanged on heating in benzene alone for 50 hr at 80°.

A solution of 330 mg (1.02 mmol) of **1c** and 115 μl (88 mg, 1.00 mmol) of tetramethylhydrazine in 5 ml of *t*-butyl alcohol (distilled from sodium metal) was degassed, sealed in a tube, and heated for 6 hr at 80 ± 3°. The resulting solution was evaporated; the crystals, 295 mg (0.92 mmol, 89%), were identified as **3c** by mp 110–113°, mmp 114–116°, and ir spectrum identical with an authentic one. When **1c** was heated alone in *t*-butyl alcohol for 6 hr 20% was consumed. (A band in the 1675–1700-cm^{-1} region appeared which roughly accounted for all the **1c** consumed.)

A solution of 323 mg (1.00 mmol) of **1c** and 88 mg (1.00 mmol) of tetramethylhydrazine in 5.00 ml of acetonitrile (dried over P_2O_5 and distilled on a Teflon spinning-band column) was heated for a total of 18 hr at 80° in one large and several small capillary tubes to produce yellow solutions. A small amount of **1c** was consumed. Approximately the same degree of consumption was observed when **1c** was heated in acetonitrile in the absence of the hydrazine.

Attempted Reaction of Di-*t*-amyldiaziridinone, 1b, with Tetramethylhydrazine.—A solution of 30 μl (23 mg, 0.26 mmol) of tetramethylhydrazine[19] and 45 mg (0.23 mmol) of diaziridinone **1b** in 2.0 ml of benzene was heated at 80° for 18 hr in tubes sealed under vacuum. Analysis of ir spectra indicated no consumption of diaziridinone or appearance of any new bands. No reaction was observed by ir when a solution of equimolar amounts of each component was heated at 80° for 12 hr, without solvent.

Reaction of 1-*t*-Butyl-2-(2-methyl-3-phenyl-2-propyl)diaziridinone, 1d, with Di-*t*-butylhydrazine 2a.—A solution of 0.876 g (3.56 mmol) of **1d**[1a] and 0.573 g (3.98 mmol) of **2a** in 5 ml of benzene was degassed, sealed in tubes, and heated at 80°. Reaction was complete in 2.5 hr. Separation of the crystals and recrystallization from benzene afforded 0.32 g (1.31 mmol, 41%) of 1-*t*-butyl-2-(2-methyl-3-phenyl-2-propyl)urea: mp 164–165°, mmp 163–165°, ir and nmr identical with authentic spectra. Fractional recrystallization of material from the filtrates afforded 0.19 g (0.77 mmol, 24%) of N-*t*-butylcarbamyl-2,2-dimethyl-3-phenylaziridine, **3d**, mp 175–176°, identical in ir and nmr with the synthetic sample. Analysis by nmr of an aliquot of the original solution of products from the reaction showed that 50% urea and 50% **3d** were formed. A parallel experiment with 0.172 g (0.70 mmol) of **1d** and 0.185 g (1.28 mmol) of **2a** in 4 ml of benzene assayed by nmr indicated 47% urea and 53% **3d**.

Reaction of Diaziridinone 1d with 1,2-Dimethylhydrazine.—A solution of 0.29 g (1.18 mmol) of **1d** and 0.24 g (4.0 mmol) of 1,2-dimethylhydrazine was degassed, sealed, and left at 25° for 24 hr. Removal of volatile components left 0.287 g (98% yield) of 1-*t*-butyl-3-(2-methyl-3-phenyl-2-propyl)urea, mp 163–165°, identical in ir and nmr with authentic material. A solution of **1d** (0.015 *M*) and 1,2-dimethylhydrazine (0.033 *M*) in benzene afforded the urea in 87% and **3d** in 13% yield.

Registry No.—1-*t*-Butyl-3-(2-methyl-3-phenyl-2-propyl)urea, 19656-66-7; **1d**, 19656-67-8; 1,2-di-*t*-amylhydrazine, 19713-61-2; 2,2′-dimethyl-2,2-azobutane, 19694-12-3; **3a**, 19656-68-9; **3b**, 19656-69-0; **3c**, 19656-70-3; **3d**, 19656-77-0.

Diaziridinones. IV.[1] Formation by Condensation of Alkyl Isocyanide with Nitrosoalkane. Evidence for a Carbodiimide N-Oxide

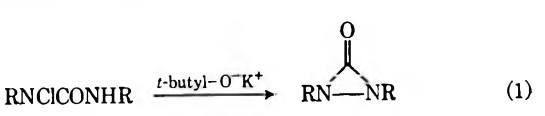
FREDERICK D. GREENE AND JOSÉ F. PAZOS

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

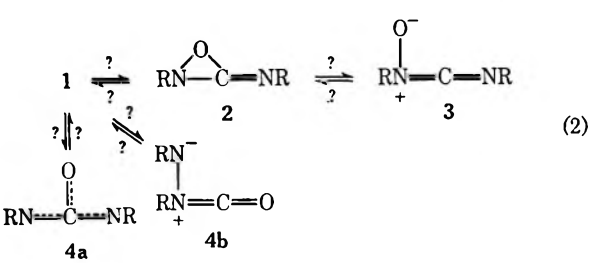
Received August 26, 1968

Reaction of *t*-butyl isocyanide with 2-methyl-2-nitrosopropane, **5**, at 70° (1:1, neat) affords di-*t*-butyldiaziridinone, **1a** (90%), di-*t*-butylcarbodiimide, **6a** (10%), and 2-methyl-2-nitropropane, **7**. The ratio of **6a**:**1a** increases with increasing concentrations of nitrosoalkane **5**; products **6a** and **7** are formed in comparable amounts over wide variation in the ratio of reactants. Reaction of *t*-butyl isocyanide with nitrosoalkane **5** in the presence of phenyl isocyanate affords two 1:1:1 adducts, **9** and **10**. Reaction of isopropyl isocyanide and nitrosoalkane **5** affords 1-*t*-butyl-2-isopropyldiaziridinone, **1b**, carbodiimide **6b**, and nitroalkane **7** in the absence of phenyl isocyanate, and affords 1:1:1 adduct **8** in the presence of phenyl isocyanate. The results are discussed in terms of condensation of alkyl isocyanide with nitrosoalkane to afford carbodiimide N-oxide **3**. This intermediate may rearrange (presumably *via* oxaziridinimine **2**) to diaziridinone **1**, may react with nitrosoalkane leading to carbodiimide **6** and nitroalkane **7**, or may react with phenyl isocyanate to afford the 1:1:1 adducts.

We recently described a synthesis (eq 1) of diaziridinones **1** and outlined some of the physical and chemical properties of this system.[2] The method of synthesis was only successful when R was a tertiary alkyl group. In a search for other methods of synthesis of **1** we have considered approaches based on the possibility of ring–chain isomerism in the diaziridinone system (eq 2). If diaziridinones were more stable than forms such as **2**, **3**, or **4**, then compounds of structure **1** might be made *via* syntheses of these other species. Inspection of **2** and **3** reveals the possibility of their formation from an isocyanide and a nitroso compound. This paper describes the results of a study of reaction of 2-methyl-2-nitrosopropane with alkyl isocyanides.[3]



(1)



(2)

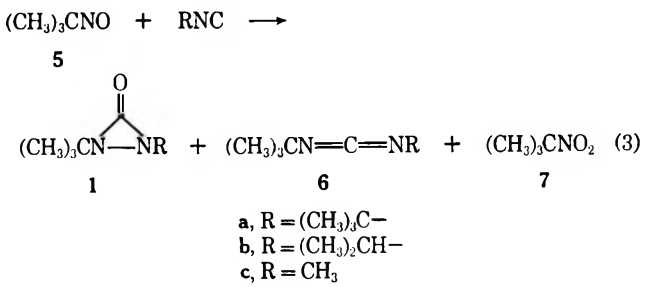
(1) (a) Part III: F. D. Greene, W. R. Bergmark, and J. G. Pacifici, *J. Org. Chem.*, **34**, 2263 (1969); (b) Financial support from the National Science Foundation (Grant No. GP 5527) is gratefully acknowledged.

(2) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969).

(3) For a report of the reaction of nitrosotrifluoromethane with methyl isocyanide, see S. P. Makarov, *et al.*, *Dokl. Akad. Nauk SSSR*, **142**, 596 (1962).

Results

2-Methyl-2-nitrosopropane **5** reacts with aliphatic isocyanides at moderate temperatures. The main products are diaziridinones **1**, carbodiimides **6**, and nitroalkane **7** (eq 3). The relative yields of products



(3)

are affected by substituents, concentration, and temperature. Diaziridinone (**1**) corresponds to a 1:1 stoichiometry of nitroso compound and alkyl isocyanide; carbodiimide (**6**) and nitroalkane (**7**), formed in comparable amounts, correspond to a 2:1 stoichiometry of the reactants.

Effect of R in RNC.—Use of *t*-butyl isocyanide with **5** results in good yields of di-*t*-butyldiaziridinone **1a**. From isopropyl isocyanide, diaziridinone **1b** was isolated and characterized although purification was difficult. Neat mixtures of **5** with *sec*-butyl isocyanide or with cyclohexyl isocyanide at 100° yielded approximately equal amounts of diaziridinone and carbodiimide (**1** and **6**, R = *sec*-alkyl) based on spectral data. Under comparable conditions *t*-butyl isocyanide and **5** afforded **1a** and **6a** in the ratio of 10:1. Reaction of methyl isocyanide with **5** afforded **6c** and **7**, with infrared evidence for the presence of diaziridinone **1c**.

The effect of temperature was examined briefly in the reaction of **5** with *t*-butyl isocyanide and with isopropyl isocyanide. An increase in temperature produced an increase in the ratio of diaziridinone to carbodimide.

A product study as a function of reactant concentrations was made for the reaction of the nitrosoalkane **5** with *t*-butyl isocyanide (Table I).

TABLE I

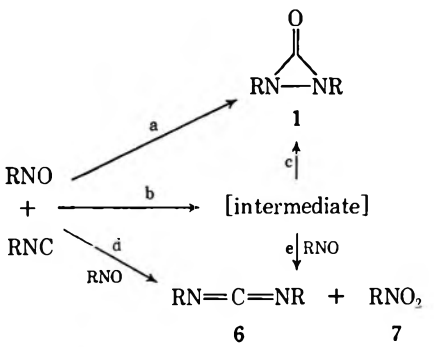
REACTION OF 2-METHYL-2-NITROSOPROPANE (**5**) WITH *t*-BUTYL ISOCYANIDE AT 70°, 75 HR

Reactants, mole fraction		Yield of products, %		
		Diaziridinone	Carbodiimide	Nitroalkane
RNO	RNC	**1a**	**6a**	**7**
0.5	0.5	90	10	10
0.05[a]	0.05[a]	50	1	1
0.1	0.9	95	2.7	3.0
0.9	0.1	65	32	35

[a] In chlorobenzene.

Di-*t*-butyldiaziridinone does not react with 2-methyl-2-nitrosopropane, excluding this possible path for formation of carbodiimide and nitroalkane. The diaziridinone is also unreactive with alkyl isocyanides under the reaction conditions. The principal findings (Table I) are as follows: (1) carbodiimide and nitroalkane are formed in comparable amounts over wide variation in ratio of reactants; and (2) the ratio of carbodiimide to diaziridinone is dependent on the concentration of nitrosoalkane. The ratio of **6**:**1** increases with increasing concentration of the nitrosoalkane; *i.e.*, the carbodiimide-forming reaction is of higher order in the nitrosoalkane than is the diaziridinone-forming reaction.

This evidence is suggestive of the possibilities summarized in eq 4. The involvement of an intermediate



(4)

seemed attractive to us since, indeed, this possibility had been the original basis for trying the experiment. The major possibilities considered for an intermediate were an oxaziridinimine, **2**, and a carbodiimide N-oxide, **3**. The latter appeared to offer the simplest routes to all three products—**1** by intramolecular rearrangement (eq 4, path c) and **6** and **7** by reaction with the nitrosoalkane (eq 4, path e). Consequently, a suitable trapping agent for the suspected intermediate was sought.

Trapping Experiments.—The necessary aspect appeared to be a 1,3-dipolarophile which would react with **3**, but not with nitrosoalkane, alkyl isocyanide, or diaziridinone. Of a number of possible trapping agents examined, isocyanates appeared to be the best. Control experiments showed that phenyl isocyanate was unreactive toward nitrosoalkane, alkyl isocyanide, and diaziridinone. Also, the rate of disappearance of the reactants was approximately the same in the presence or absence of phenyl isocyanate. However, the product composition was completely altered. Diaziridinone, carbodiimide, and nitroalkane were absent; in their place was a mixture of products, some of which were rather labile. From isopropyl isocyanide, 2-methyl-2-nitrosopropane (**5**), and phenyl isocyanate was isolated a crystalline compound corresponding to a 1:1:1 adduct, **8**. From *t*-butyl isocyanide, nitrosoalkane **5**, and phenyl isocyanate were isolated two 1:1:1 adducts (**9** and **10**) and a third adduct, **11**, of composition $C_{18}H_{19}N_3O_2$ corresponding formally to a 1:1:1 adduct of *phenyl* isocyanide, **5**, and phenyl isocyanate. From the reaction of *t*-butyl isocyanide, nitrosoalkane **5**, and *t*-butyl isocyanate was isolated a 1:1:1 adduct, **12**. Of principal consequence to the present paper is the formation of the 1:1:1 adducts. The number of possible structures is large. Both the structures and the reactions of these adducts pose many questions on which we hope to report at a later date. A summary of information and tentative structural assignments are given in the following section.

Nature of the 1:1:1Ad ducts.—Physical data are summarized in Table II. The principal mode of mass spectral fragmentation of the adducts[4,5] involves the

(4) The full mass spectral data are reported in ref 5.

(5) J. F. Pazos, Doctoral Dissertation, Massachusetts Institute of Technology, Cambridge, Mass., 1967.

TABLE II

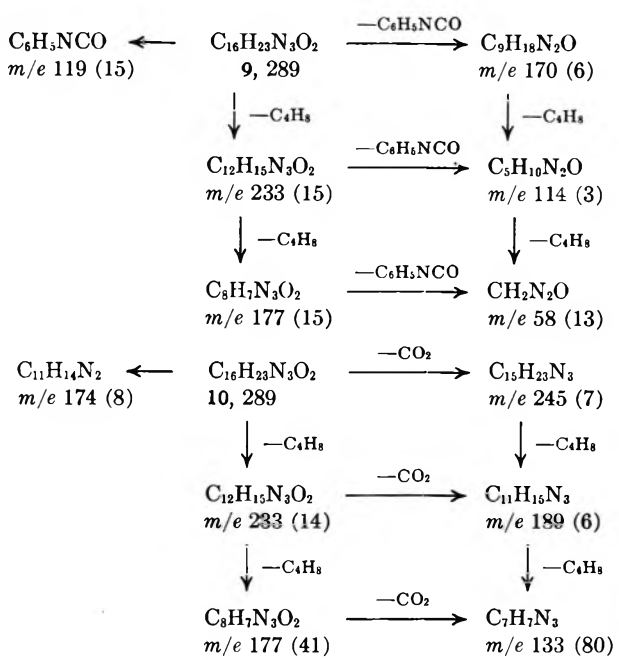
PHYSICAL DATA FOR 1:1:1 ADDUCTS OBTAINED FROM REACTION OF 2-METHYL-2-NITROSOPROPANE WITH ALKYL ISOCYANIDE IN THE PRESENCE OF PHENYL ISOCYANATE

	8	9	10	11	12
Mp, °C	85.5–86	80–88 dec	70–71.5	105–106	104–106
Ir (CCl_4), cm^{-1}	1815 (2), 1715 (3)	1775 (1), 1700 (5)	1815 (2), 1716 (3)	1810 (vs), 1690 (vs)	1790 (s), 1700 (vs)
Nmr (CCl_4), ppm	1.13 (s, 9 H), 1.23 (d, 6 H), 3.87 (septuplet, 1 H), 7.3 (m, 5 H)	1.32 (s, 9 H), 1.40 (s, 9 H), 7.25 (d, 5 H)	1.27 (s, 9 H), 1.34 (s, 9 H), 7.1–7.6 (m, 5 H)	1.55 (s, 9 H), 6.4–6.9 (m, 5 H), 7.05 (s, 5 H)	1.25 (s, 9 H), 1.34 (s, 9 H), 1.55 (s, 9 H)
Uv, λ, mμ (ε) (isooctane)	238 (11, 380)	243 (11,960) 276 sh (1,715), 284 sh (935)	238 (11,320)	263 (6,540) plateau on end absorption	End absorption
Mass spectrum[a] ion, *m/e* (relative intensity)	275, 260 (3), 231 (13), 219 (100), 177 (18), 175 (37), 160 (13), 133 (82), 119 (17), 118 (12), 105 (27), 104 (35), 92 (58), 77 (72), 57 (76)	289 (0.7), 245 (zero), 233 (15), 218 (8), 177 (15), 170 (6), 119 (15), 114 (3), 93 (7), 91 (11), 84 (15), 83 (15), 58 (13), 57 (100)	289, 245 (7), 233 (14), 189 (6), 177 (41), 174 (8), 133 (80), 119 (8), 118 (7), 105 (10), 93 (22), 91 (20), 83 (26), 77 (26), 57 (100)	309 (18), 265 (7), 253 (100), 209 (48), 208 (85), 207 (18), 194 (7), 134 (10), 118 (40), 109 (115), 92 (44), 77 (46), 65 (15), 57 (48)	269, 213 (7), 157 (19), 142 (34), 135 (10), 133 (8), 113 (12), 101 (29), 98 (40), 89 (12), 74 (7), 68 (11), 58 (42), 57 (100)

[a] References 4 and 5.

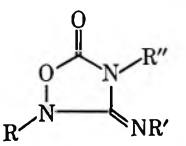
loss of isobutylene (McLafferty rearrangement). For adducts **8**, **10**, and **11**, loss of carbon dioxide is observed both as a primary process and as a secondary process (after loss of one or more isobutylene units). Fragments of composition corresponding to isopropylphenylcarbodiimide, *t*-butylphenylcarbodiimide, and diphenylcarbodiimide also are obtained from **8**, **10**, and **11**, respectively. Adduct **9** (isomeric with **10**) shows loss of isobutylene but no primary loss of carbon dioxide. It also affords a positive ion at M − C_6H_5NCO. Adduct **10** shows no ion at M − C_6H_5NCO. The positive ions corresponding to C_6H_5NCO and $(CH_3)_3CNCO$ are much larger from **9** than from **10**. The main mass spectral fragmentation patterns for **9** and **10** are summarized in Scheme I.

SCHEME I



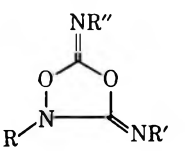
Adduct **9** could only be isolated when the reaction was carried out at 40° and worked up after 10% reaction. It decomposed in 10 min at 100°. Thermal decomposition of **9** in dilute solution afforded **10**, diaziridinone **1a**, and phenyl isocyanate. When excess phenyl isocyanate was added to a solution of **9** in acetonitrile before heating, no diaziridinone was formed.

Adducts **8**, **10**, and **11**, similar in ir, uv, and mass spectral fragmentation patterns, are tentatively assigned structure A, the substituted 3-imino-1,2,4-oxadiazolinone-5. Adduct **9** is tentatively assigned structure B, the substituted 2,5-diimino-1,3,4-dioxazolidine.



A

8, R = $(CH_3)_3C$; R′ = $(CH_3)_2CH$; R″ = C_6H_5
10, R = $(CH_3)_3C$; R′ = $(CH_3)_3C$; R″ = C_6H_5
11, R = $(CH_3)_3C$; R′ = C_6H_5; R″ = C_6H_5



B

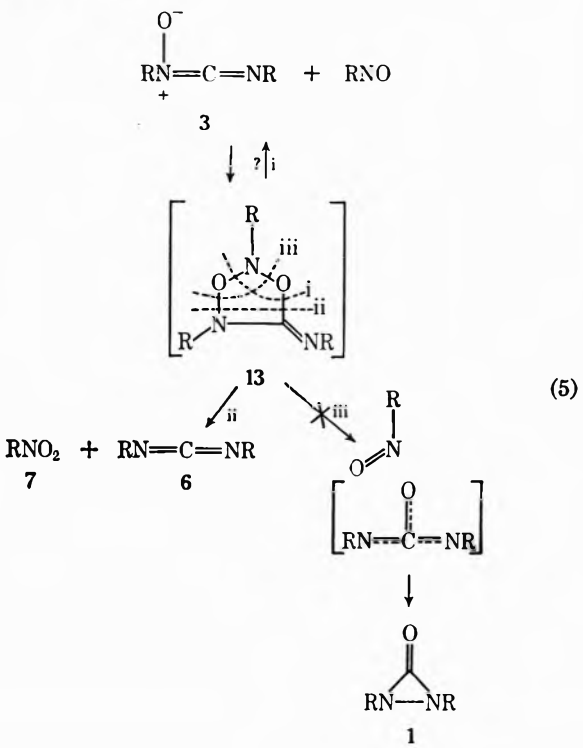
9, R = $(CH_3)_3C$; R′ = $(CH_3)_3C$; R″ = C_6H_5

$C_2N_3O_2RR'R''$
12, R = R′ = R″ = $(CH_3)_3C$
(structure unassigned)

Conclusions from Trapping Experiments.—The absence of diaziridinone **1**, carbodiimide **6**, and nitroalkane **7** from the product mixture when nitrosoalkane reacts with alkyl isocyanide in the presence of phenyl isocyanate, coupled with the absence of an effect of isocyanate on rate, provides compelling evidence for an intermediate. This evidence excludes the formation of diaziridinone by a direct bimolecular reaction of nitrosoalkane and alkyl isocyanide (Scheme I, path a). It also excludes the formation of nitroalkane and carbodiimide by a direct termolecular reaction (Scheme I, path d).

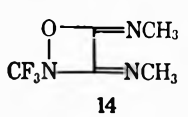
For the structure of the intermediate, we favor the carbodiimide N-oxide, **3**, on the basis of the high reactivity toward 1,3-dipolarophiles. Covalent structure **2** cannot be excluded for the trappable intermediate, but it would not appear to be a reactive "dipolar species." (Compare also nitrones and oxaziridines in cycloaddition reactivity.)[6,7]

We return now to the question of mode of formation of carbodiimide **6** and nitroalkane **7** (eq 3). These products, formed in equal amounts, might arise by single oxygen transfer from **3** to nitrosoalkane **5**. An attractive alternative (eq 5) is 1,3-dipolar cycloaddition of **3** and nitrosoalkane yielding **13**. Decomposition of **13** by retrocycloaddition path ii would give **6** and **7**. An alternate mode of decomposition, path iii, formally *could* lead to **1**. However, the variation in product composition with changes in reactant concentrations (Table I) indicates that the formation of products **6** and **7** is of higher order in nitrosoalkane than the formation of **1**. Thus, path iii would not appear to be an important route to **1**.



(5)

The reaction of nitrosotrifluoromethane with methyl isocyanide[3] affords an adduct of composition $2CH_3NC + 1CF_3NO$ to which structure **14**, 2-trifluoromethyl-3,4-di(methylimino)-1,2-oxazetidine, has been assigned on the basis of its pyrolysis (400°) to methyl isocyanate and N-methyl-N′-trifluoromethylcarbodiimide. Adduct **14** may be formed by capture of an intermediate carbodiimide N-oxide by methyl isocyanide rather than by the nitrosotrifluoromethane.

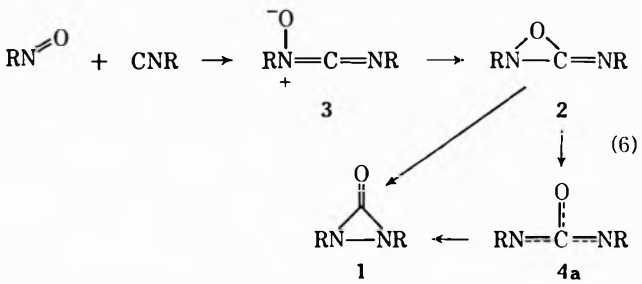


14

(6) R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of the Alkenes," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 11.

(7) E. Schmitz, "Dreiringe mit Zwei Heteroatomen," Springer-Verlag, Berlin, 1967.

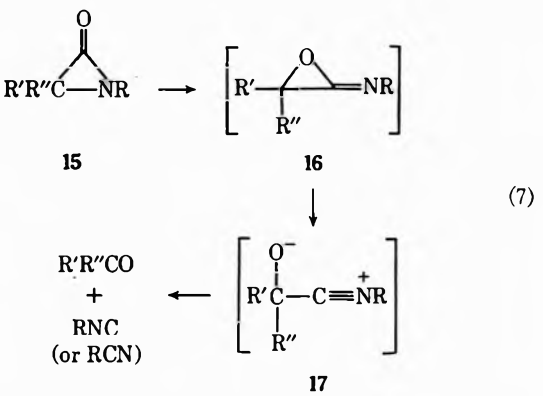
It is of interest to consider the over-all conversion of nitrosoalkane and alkyl isocyanide to diaziridinone (eq 6). As indicated above, we favor **3** for the trappable intermediate. Its isomerization to **1** would appear to require proceeding *via* **2**. At this time we have no evidence to indicate whether **2** has a finite existence or represents an energy maximum (the former seems more likely to us). Conversion of **2** to **1** may proceed directly or *via* a species such as **4a**.



(6)

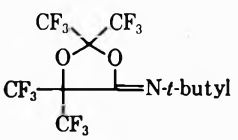
Efforts to approach **3** from **1** have been unsuccessful. Di-*t*-butyldiaziridinone may be heated with phenyl isocyanate for prolonged periods with no evidence of formation of adducts **9** or **10**. Other efforts to trap a ring-opened form of a diaziridinone have been unsuccessful.[2] Also, thermal decomposition of diaziridinones[5] does not afford nitrosoalkane, isocyanide, or nitrile (the expected thermal rearrangement product of an isocyanide).

The structurally related class, aziridinones **15**,[8] shows rather different behavior. Efforts to prepare these compounds from aldehydes or ketones and isocyanides have been unsuccessful. On the contrary, even under mild conditions some aziridinones decompose to ketones and isocyanides, presumably *via* the sequence of eq 7.[8] An important difference between **17** and **3** lies in the poorer accommodation of charges in the former compared with the latter. However, when R′ and R″ are perhaloalkyl, reaction appears to



(7)

proceed in the reverse direction; *e.g.*, hexafluoroacetone reacts with *t*-butyl isocyanide to afford the iminodioxolane, **18**, in a formal sense the product of reaction of **17** with another molecule of hexafluoroacetone.[9]



18

(8) I. Lengyel and J. C. Sheehan, *Angew. Chem.*, **80**, 27 (1968).

(9) W. J. Middleton, D. C. England, and C. G. Krespan, *J. Org. Chem.*, **32**, 948 (1967).

In the presence of acids, reaction occurs between isocyanides and aldehydes (or ketones) affording α-acyloxyamides (the Passerini reaction).[10] That reaction does not require, nor is it likely to involve, species such as **16** or **17** as *discrete* intermediates. Some evidence in support of species such as **17**, **16**, and **15** is found in the reactions of ketones and isocyanides in the presence of boron trifluoride.[11a,b] Isolation of both isomeric forms, **15** and **16**, has been reported for R = *t*-butyl, R′ = 1-adamantyl, R″ = H. Both compounds decompose to R′CHO and RNC; **16** undergoes the change at room temperature, **15** at 140° (presumably *via* **16**).[11c]

Experimental Section

All melting points are corrected. All melting points of 1,3-di-*t*-butylurea were taken in tubes sealed under vacuum. Nuclear magnetic resonance spectra were determined at 60 Mc; signals are reported in parts per million (ppm) downfield from tetramethylsilane. Gas–liquid partition chromatographic analyses (glpc) were performed on Aerograph Models 200 and A-700 (Autoprep) using a helium carrier gas and thermal conductivity detectors with the following columns: column D [a 10 ft × 0.25 in. glass column packed with 20% Carbowax 20 on Chromosorb W (washed to pH 8) diatomite support]; column E [a 5 ft × 0.25 in. stainless steel tube packed with 20% SE-30 silicone oil on 60/80 mesh Chromosorb W]. All identifications unless otherwise noted of glpc components were made by the identity with an authentic sample of both retention time and ir spectrum of a collected sample. All quantitative analyses were made by the internal standardization method unless otherwise noted.

Alkyl isocyanides were prepared by published methods[12,13] (the former[12] gave better results, and handling of the isocyanides was reduced to a minimum): methyl isocyanide,[12b] ir 2165 cm^{-1}; isopropyl isocyanide, bp 87° (lit.[13] bp 87°); *t*-butyl isocyanide, bp 91° (lit.[13] bp 91°). The isocyanides were obtained in 99% purity, analyzed by glpc on column E.

N-*t*-Butylhydroxylamine.—To a mixture of 2-methyl-2-nitropropane[14] (199.5 g, 1.94 mol) and a solution of ammonium chloride (83.2 g in 3.2 l. of water) cooled to 10° with an ice bath was added 274 g of zinc in small portions over 1 hr, never letting the temperature rise above 20°. The mixture was stirred 1 additional hr at 0° and 30 min at room temperature. The reaction mixture was filtered and the solid was washed with 1 l. of boiling water. The filtrate was made basic with sodium hydroxide, and potassium carbonate (1.36 kg) was added. The aqueous layer was extracted with three 500-ml portions of ether. The ether was dried ($MgSO_4$) and evaporated, yielding 118 g (68%) of *t*-butylhydroxyamine: mp 60–62° (lit.[15] mp 64–65°).

2-Methyl-2-nitrosopropane was prepared by the method of Emmons,[15] mp 66–67° when heated at 2°/min (lit.[15] mp 79–81°), not changed by recrystallization or sublimation, and 99% pure by glpc analysis (column E).

Anal. Calcd for C_4H_9NO: C, 55.14; H, 10.41. Found: C, 55.00; H, 10.44.

Di-*t*-butylcarbodiimide had bp 60° (17 mm) [lit.[16] bp 51° (10 mm)]; ir 2090, 2125 cm^{-1}.

1-*t*-Butyl-2-isopropyldiaziridinone, 1b, from Isopropyl Isocyanide and 2-Methyl-2-nitrosopropane.—A sealed tube containing 0.2 g (2.3 mmol) of 2-methyl-2-nitrosopropane and 0.2 g (2.9 mmol) of isopropyl isocyanide was heated at 130° for 20 min. The ir spectrum of the crude reaction mixture indicated absorption at 1870 (diaziridinone), at 2100, 2130, (carbodiimide), and at 1540, 1350 cm^{-1} (nitroalkane). The material was distilled (trap to trap) and gas chromatographed (column D) at 45° and 20 lb of helium pressure. Collection of the major peak gave pure diaziridinone **1b**: ir (CCl_4) 1900 sh, 1880 s, 1850 cm^{-1} sh; nmr (CCl_4) δ 1.03 (singlet with shoulder at 1.1, 15 H), 2.82 (septuplet, 1 H).

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found: C, 61.86; H, 10.31; N, 17.92.

Reaction of Methyl Isocyanide with 2-Methyl-2-nitrosopropane.—A tube containing 0.0169 g (0.194 mmol) of 2-methyl-2-nitrosopropane, 0.0044 g (0.107 mmol) of methyl isocyanide, and 0.0078 g of *t*-butylbenzene (glpc standard) was sealed and heated to 100° for 3 hr. The reaction mixture was analyzed by glpc on column E. The principal products, N-*t*-butyl-N′-methylcarbodiimide[16] (retention time at 100°, 6.2 min) and 2-methyl-2-nitropropane[14] (retention time at 100°, 4.4 min), were collected and identified by ir: yields, 60 ± 5% carbodiimide and 45 ± 5% *t*-$BuNO_2$. Examination by ir of a reaction of methyl isocyanide and the nitrosoalkane, **5** (in a ratio of 1.5:1), heated at 121° for 18 min showed weak absorption at 1860, attributed to N-methyl-N′-*t*-butyldiaziridinone **1c**.

Product Study for the Reaction of 2-Methyl-2-nitrosopropane and *t*-Butyl Isocyanide.—The reactions were run in sealed tubes. Purified chlorobenzene (better than 99% by glpc) was used as an internal standard. Standard solutions for all reactions (with approximate concentrations expected for the products) were prepared from the pure compounds, di-*t*-butyldiaziridinone,[2] di-*t*-butylcarbodiimide,[16] and 2-methyl-2-nitropropane.[14] Standard solutions with concentrations of di-*t*-butyldiaziridinone (**1a**) near the expected value were used because of the nonlinearity of the response factor of diaziridinone with concentration. The analyses were made on column E by temperature programming (6°/min; flow, 60 ml/min; initial temperature, 25°). The temperatures at which the components were observed are given in parentheses: *t*-Bu-NO (30°), *t*-Bu-NC (40°), *t*-Bu-NO_2 (62°), di-*t*-butylcarbodiimide (105°), di-*t*-butyldiaziridinone (113°). The results are summarized in Table I.

Reaction of Phenyl Isocyanate, 2-Methyl-2-nitrosopropane, and *t*-Butyl isocyanide. A. At 40° for 140 Hr.—2-Methyl-2-nitrosopropane (10.0 g, 0.115 mol), *t*-butyl isocyanide (9.0 g, 0.108 mol), and phenyl isocyanate (13.0 g, 0.109 mol) were heated at 40° for 140 hr in a tightly stoppered vessel. Examination of the crude mixture by ir indicated strong absorption at 1810, 1700, and much weaker absorption at 1775 cm^{-1}. The crude mixture was then heated to 100° for 5 min after which no 1775-cm^{-1} absorption remained. Aft r evaporation of the volatile material, 10.6 g of oil remained. Fractional crystallization from hexane afforded two compounds, **11** and **10**. Compound **11** was less soluble in hexane and was the first material to crystallize. Purification was accomplished by one further recrystallization, affording 1.851 g of pure **11**: mp 105–106°; physical data are reported in Table II.

Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.11; H, 6.20; N, 13.27.

Although ir indicated **10** was the main component left in the reaction mixture, repeated recrystallizations were needed to isolate a pure sample. Final purification by fractional sublimation under high vacuum at 60° afforded compound **10** as a white crystalline solid, mp 70–71.5°; physical data are reported in Table II.

Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.18; H, 8.06; N, 14.34.

B. At 40° for 30 Hr.—2-Methyl-2-ni rosopropane (3.014 g, 0.0346 mol), *t*-butyl isocyanide, (2.999 g, 0.036 mol), and phenyl isocyanate (0.6466 g, 0.0054 mol) were heated at 40° for 30 hr in a stoppered vessel. Analysis of the crude reaction mixture by glpc (column E) indicated no diaziridinone **1a** and very little phenyl isocyanate present. The ir of the crude mixture showed absorption at 1775 and 1700, but no bands at 1810 cm^{-1}. The volatile materials were evaporated under high vacuum at room temperature. The residual oil (1.251 g) was crystallized from hexane affording 0.341 g (1.8 mmol, 33%) of **9** (dec pt 77–88°). Recrystallization from pentane afforded 0.126 g of material of **9**, dec pt 80–88°; physical data are reported in Table II.

Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.70; H, 8.17; N, 14.56.

Thermal Decomposition of 9.—Solutions of **9** (1%) in carbon tetrachloride, isooctane, chloroform, and acetonitrile were sealed and heated for 10 min at 100°. The prominent bands in the ir

(10) See I. Hagedorn and U. Eholzer, *Chem. Ber.*, **98**, 936 (1965), and references cited therein.

(11) (a) T. Saegusa, N. Taka-ishi, and H. Fujii, *Tetrahedron*, **24**, 3795 (1968); (b) H.-J. Kabbe, *Angew. Chem. Intern. Ed. Engl.*, **7**, 389 (1968); (c) K. Bott, *Tetrahedron Lett.*, 3323 (1968)

(12) (a) J. Casanova, Jr., R. E. Schuster, and N. D. Werner, *J. Chem. Soc.*, 4280 (1963); (b) R. E. Schuster, J. E. Scott, and J. Casanova, Jr., *Org. Syn.*, **46**, 75 (1966).

(13) I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).

(14) N. Kornblum, *Org. Reactions*, **12**, 133 (1962).

(15) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739, 6522 (1957).

(16) E. Schmidt, W. Striewsky, and F. Hitzler, *Ann.*, **560**, 222 (1948); E. Schmidt and M. Seefelder, *ibid.*, **571**, 83 (1951).

at 1775 and 1700 cm^{-1} of **9** were replaced by absorption at 2250 (isocyanate), at 1870 (diaziridinone **1a**), and at 1810 and 1710 cm^{-1} (10). In carbon tetrachloride and isooctane, **10** predominated. In chloroform and acetonitrile, **1a** predominated. From the acetonitrile reaction diaziridinone **1a** was also observed as the major component by glpc, and identified by collection and comparison with authentic material. Addition of phenyl isocyanate to the acetonitrile solution of **9** before heating completely inhibited diaziridinone formation.

Reaction of Isopropyl Isocyanide, 2-Methyl-2-nitrosopropane, and Phenyl Isocyanate.—Isopropyl isocyanide (0.0291 mol), 2-methyl-2-nitrosopropane (0.0279 mol), and phenyl isocyanate (0.0321 mol) were placed in a pressure bottle and heated to 100° for 5 hr and 40 min. Upon cooling crystallization occurred. The volatile materials were removed under high vacuum. The solid residue (6 g) was fractionally crystallized from hexane, affording 1 g (0.003 mol, 11% yield) of pure **8**, mp 85.5–86°; physical data are reported in Table II.

Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.58; H, 7.78; N, 15.13.

Reaction of *t*-Butyl Isocyanide, 2-Methyl-2-nitrosopropane, and *t*-Butyl Isocyanate.—A tube containing 2.010 g (0.023 mol) of 2-methyl-2-nitrosopropane, 2.643 g (0.032 mol) of *t*-butyl isocyanide, and 4.660 g (0.047 mol) of *t*-butyl isocyanate was degassed, sealed under vacuum, and heated for 118 hr at 65°. After breaking the seal, the crude mixture was trap-to-trap distilled (25°, 0.01 mm) leaving 1.803 g of nonvolatile material. The ir of the crude residue indicated some diaziridinone **1a**, but very strong absorption was present at 1700 and 1790. The material was dissolved in hexane and crystallized at −10° affording 0.498 g (0.00185 mol, 8% yield) of **12**, mp 104–106°; physical data are reported in Table II.

Anal. Calcd for $C_{14}H_{27}N_3O_2$: C, 62.42; H, 10.11; N, 15.60; mol wt, 269. Found: C, 62.13; H, 10.06; N, 15.64; mol wt, 266 (osmotic in chloroform).

Control Experiments. Attempted Reaction of 2-Methyl-2-nitrosopropane with Di-*t*-butyldiaziridinone, 1a.—A sealed tube contained 26.2 mg (0.15 mmol) of diaziridinone **1a** and 13.7 mg (0.16 mmol) of 2-methyl-2-nitrosopropane was heated at 100° for 33 hr. Comparison of the ir before and after heating indicated no change had occurred.

Attempted Reaction of Methyl Isocyanide with Di-*t*-butyldiaziridinone.—Methyl isocyanide (4.5 mg, 0.11 mmol) and di-*t*-butyldiaziridinone (8 mg, 0.047 mmol) were sealed in a capillary and heated at 100° for 2 hr. Analysis by ir indicated that no reaction had occurred.

Attempted Reaction of Phenyl Isocyanate with Di-*t*-butyldiaziridinone, 1a.—Phenyl isocyanate (0.381 g, 3.204 mmol) and di-*t*-butyldiaziridinone, **1a** (0.422 g, 2.484 mmol), were mixed and an aliquot was sealed in a capillary tube. The tube was heated to 100° for 5.5 hr. Comparison of ir before and after heating indicated that no reaction had taken place.

Attempted Reaction of Phenyl Isocyanate with 2-Methyl-2-nitrosopropane.—Phenyl isocyanate (0.643 g, 5.41 mmol), 2-methyl-2-nitrosopropane (0.247 g, 2.84 mmol), and chlorobenzene (1.29 g) were sealed and heated for 9 hr at 100°. Analysis on column E indicated 2.02 mmol (71%) of nitroso-*t*-butane and 5.14 mmol (95%) of phenyl isocyanate.

Attempted Reaction of Phenyl Isocyanate with *t*-Butyl Isocyanide.—Phenyl isocyanate (0.624 g, 5.33 mmol), *t*-butyl isocyanide (0.254 g, 3.06 mmol), and chlorobenzene (1.173 g) were sealed and heated for 9 hr at 100°. Analysis on column E indicated 2.60 mmol (85%) of *t*-butyl isocyanide and 5.33 mmol (100%) of phenyl isocyanate.

Reaction of 2-Methyl-2-nitrosopropane and *t*-Butyl Isocyanide in the Presence and Absence of Phenyl Isocyanate. Solution A.—2-Methyl-2-nitrosopropane (0.183 g, 2.103 mmol), *t*-butyl isocyanide (0.190 g, 2.90 mmol), and phenyl isocyanate (0.738 g, 6.205 mmol) were diluted to 2 ml with chlorobenzene (0.925 g).

Solution B.—2-Methyl-2-nitrosopropane (0.184 g, 2.105 mmol) and *t*-butyl isocyanide (0.190 g, 2.90 mmol) were diluted to 2 ml with chlorobenzene (1.646 g).

Aliquots of solutions A and B were sealed in capillary tubes and heated to 100°. Tubes were taken out at intervals and analyzed by glpc (column E) for *t*-BuNO, *t*-BuNC, and diaziridinone, **1a**. The error in the analysis of *t*-BuNO and *t*-BuNC was ±10% owing to the short retention times and small areas. Within this limit of error, the rate of disappearance of *t*-BuNO and *t*-BuNC was not affected by the presence of phenyl isocyanate. Analysis after 4.5 hr gave the following percentages (in parentheses): solution A—*t*-BuNO (50), *t*-BuNC (60), and Dz (0.7); solution B—*t*-BuNO (35), *t*-BuNC (45), and Dz (45).

Registry No.—**1b**, 19656-61-2; **8**, 19656-62-3; **9**, 19656-64-5; **10**, 19656-63-4; **11**, 19656-65-6.

Acknowledgment.—The authors are indebted to Dr. Istvan Lengyel for the mass spectral data and for assistance in their interpretation.

The Dehydration of N-Arylmaleamic Acids with Acetic Anhydride

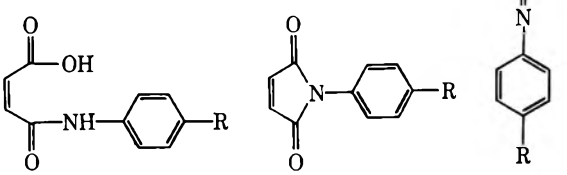
CAROL K. SAUERS

Department of Chemistry, Douglass College, Rutgers, The State University, New Brunswick, New Jersey 08903

Received December 3, 1968

Dehydrations of N-arylmaleamic acids in acetic anhydride with and without sodium acetate were studied. N-Arylmaleimides, N-arylmaleisoimides, maleic anhydride, and substituted acetanilides were detected in these reactions. Mechanisms to account for these products were discussed. The kinetics of the acetate-catalyzed rearrangement of N-arylmaleisoimides to N-arylmaleimides were investigated. This reaction was shown to be a major source of maleimides in the dehydration reactions.

A standard synthesis[1,2] for N-arylmaleimides (**2**) is the dehydration of N-arylmaleamic acids (**1**) with acetic anhydride containing sodium acetate at temperatures below 100°. Under certain conditions acetic anhydride–sodium acetate mixtures also have been found to yield isoimides (**3**). For example, N-*p*-anisylmaleamic acid (**1a**) gave N-*p*-anisylmaleisoimide (**3a**) when treated with these reagents at low temperatures, but gave imide **2a** at higher temperatures.[3] Some N-*n*-butylmaleisoimide was detected in the dehydration of N-*n*-butylmaleamic acid to the imide in acetic anhydride containing sodium acetate.[4]

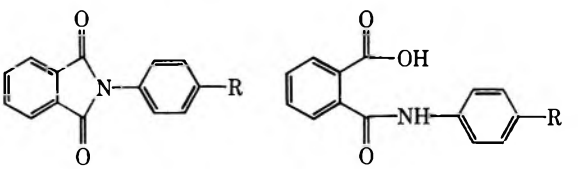


1 **2** **3**

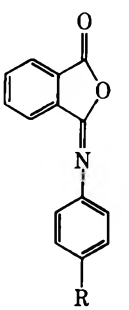
a, R = OCH_3
b, R = CH_3
c, R = H
d, R = Cl
e, R = $COCH_3$

Acetic anhydride without sodium acetate has been found to give isoimides in low yields.[5,6] Imides were also products of this reagent.[5] When this reaction was run at the temperature of refluxing acetic anhydride, acetanilide and substituted acetanilides were isolated.[2]

It has been suggested[4] that isoimides are the primary products of these dehydration reactions at moderate temperatures and that the imide products are formed by the rearrangement[3-9] of the isoimides. Roderick has shown that a major part of N-*p*-chlorophenylphthalimide (**4b**) formed in the acetic anhydride–sodium acetate dehydration of N-*p*-chlorophenylphthalamic acid (**5b**) must be formed directly.[5] Rearrangement of N-*p*-chlorophenylphthalisoimide (**6b**) under the conditions of the reaction was not sufficiently rapid to account for the yields of imide obtained.



4 **5**



6

a, R = H
b, R = Cl

We wished to study the dehydrations of N-arylmaleamic acids (**1**) to determine the effect of substituents on the benzene ring upon the products of the reactions. We also wished to study the effects of substituents upon the rate of the acetate-catalyzed rearrangement of N-arylmaleisoimides (**3**) to N-arylmaleimides (**2**). Results of such experiments would determine whether or not imide products were formed directly in the dehydrations or were formed by rearrangement of the initially formed isoimides.

Results

When the maleisoimides (**3a–e**) were treated with acetic anhydride containing sodium acetate at temperatures from 65 to 85°, rearrangement to the corresponding maleimides (**2a–e**) occurred. The rates of these reactions were measured by observing the disappearance of the upfield isoimide olefinic proton peaks and the appearance of the olefinic proton peaks assigned to the maleimides in the nuclear magnetic resonance spectra of the reaction mixtures. The nuclear magnetic resonance spectra are summarized in Table I.

First-order rate constants were calculated for individual rate runs by the method of least squares. The standard error was below 6%. Deviation of individual runs from the average of two or more duplicate

(1) N. E. Searle, U. S. Patent 2,444,536 (1948); *Chem. Abstr.*, **42**, 7340 (1948).

(2) A. E. Kretov and N. E. Kul'chitskaya, *Zh. Obshch. Khim.*, **26**, 208 (1956); *Chem. Abstr.*, **50**, 13771 (1956).

(3) A. E. Kretov, N. E. Kul'chitskaya, and A. F. Mal'nev, *J. Gen. Chem. USSR*, **31**, 2415 (1961).

(4) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).

(5) W. R. Roderick, *ibid.*, **29**, 745 (1964).

(6) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, **31**, 1311, 1317 (1966).

(7) For thermal rearrangements in the acyclic series see (a) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965); (b) D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, **89**, 637 (1967); (c) D. J. Hoy and E. J. Poziomek, *J. Org. Chem.*, **33**, 4050 (1968).

(8) M. L. Ernst and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 5001 (1966).

(9) (a) A. Le Berre and B. Dumaitre, *C. R. Acad. Sci. Paris, Ser. C*, **266**, 334 (1968); (b) H. Feuer and J. P. Asunskis, *J. Org. Chem.*, **27**, 4684 (1962).

runs was less than ±10%. The kinetic data are summarized in Table II.

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR N-ARYLMALEISOIMIDES AND N-ARYLMALEIMIDES[a]

	Olefinic protons		Aromatic protons		
Compd	δ	J, cps	δ	J, cps	Substituent protons, δ
3a	7.47, 6.75	5.5	7.50, 6.98	9	3.82
2a	6.91		7.27, 7.03	9	3.83
3b	7.50, 6.79	5.5	7.28		2.34
2b	6.91		7.28		2.38
3c	7.54, 6.84	5.5	7.38		
2c	6.93		7.44		
3d	7.53, 6.86	5.5	7.40		
2d	6.95		7.51, 7.41	9.5	
3e	7.58, 6.92	5.5	8.05, 7.35	8.5	2.58
2e	7.00		8.11, 7.58	8.5	2.60

[a] Values for δ relative to internal tetramethylsilane in acetic anhydride.

TABLE II

RATE CONSTANTS FOR THE REARRANGEMENT OF N-ARYLMALEISOIMIDES TO N-ARYLMALEIMIDES IN ACETIC ANHYDRIDE

Expt	3, R	T, °C	M[a] of isoimide	M[b] of sodium acetate	10^5k,[c] sec^{-1}
1	OCH_3	65.0	0.383	0.024	2.7
2	OCH_3	75.0	0.329	0.024	5.2
3	OCH_3	75.0	0.413	0.039[d]	9.3
4	OCH_3	85.0	0.365	0.024	11
5	OCH_3	75.0	0.348	0	*e*
6	OCH_3	75.0	0.385	0[f]	*g*
7	CH_3	65.0	0.448	0.024	3.9
8	CH_3	75.0	0.395	0.024	7.8
9	CH_3	65.0	0.413	0.039[d]	15
10	CH_3	85.0	0.399	0.024	15
11	H	65.0	0.438	0.024	7.0
12	H	75.0	0.427	0.024	13
13	H	75.0	0.460	0.039[d]	27
14	H	85.0	0.422	0.024	31
15	Cl	65.0	0.346	0.024	19
16	Cl	75.0	0.314	0.024	38
17	Cl	75.0	0.346	0.039[d]	64
18	Cl	75.0	0.334	0	6.7
19	Cl	75.0	0.310	0.024[d]	55
20	Cl	75.0	0.345	0[f]	*h*
21	Cl	85.0	0.351	0.024	68
22	$COCH_3$	75.0	0.246	0.024	110
23	$COCH_3$	75.0	0.192	0[f]	*i*

[a] Average starting molarity of the isoimide. [b] Solutions contain 1% acetic acid except as noted otherwise. [c] Average value of the calculated first-order rate constants for two or more runs. [d] Contains 2% acetic acid. [e] 3% reaction after 100 min. [f] Freshly distilled acetic anhydride. [g] No reaction after 168 min. [h] 5% reaction after 185 min. [i] No reaction after 30 min.

The rate of the rearrangement reaction was increased in compounds with electron-deficient aromatic rings. The Hammett equation ρ value for expt 2, 8, 12, 16, and 22 is 1.7 ± 2.[10] The values for the activation energy, E_a, are 17 ± 3, 16 ± 1, 18 ± 2, and 16 ± 1 for **3a**, **3b**, **3c**, and **3d**, respectively. Sodium acetate appears to be a more potent catalyst than acetic acid (expt 2, 5, 16, and 18). Rearrangement in the solvent alone is small compared to the amount of rearrangement occurring in the presence of catalysts (expt 6, 20, and 23).

(10) Values for σ used are those listed in C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 323 (1964).

The maleimides were obtained by complete isomerization (7–10 half-lives) of the maleisoimides. No products other than the imides were isolated or detected by nmr or vpc.

The dehydrations of the N-arylmaleamic acids (**1**) in acetic anhydride were more complex than the rearrangement reactions. The reactions appeared to occur as fast as the solution of the starting maleamic acid. Total solution at 75° was slow and so the reactions were heterogeneous. Maleic anhydride and the appropriately substituted acetanilides were detected by the appearance of the peaks corresponding to these materials in the nmr spectra of the reaction mixtures. The acetanilides were isolated from the reactions of **1a–d** with acetic anhydride alone. Maleic anhydride was isolated from the dehydration of **1b** in the presence of acetic anhydride alone. The reaction mixture was treated with cyclopentadiene followed by methanol at reflux and the methyl half-ester of *endo*-norbornene-*cis*-5,6-dicarboxylic acid was obtained as the only acidic product.

The reaction mixtures were analyzed by nmr; these data are summarized in Table III.

TABLE III

PRODUCTS OF THE DEHYDRATION OF N-ARYLMALEAMIC ACIDS IN ACETIC ANHYDRIDE AT 75°

	Conditions		Distribution of products, %		
Compd	M of sodium acetate[a]	Time,[b] min	Isoimide[c]	Isoimide + imide	Maleic anhydride[d]
1a	0.024	3 (10, 245)	88 (90, 43)	87	13
1b	0.024	3 (22, 60)	85 (90, 70)	81	19
1c	0.024	3 (8, 90)	77 (80, 29)	92	8
1d	0.024	3 (16, 45)	57 (48, 15)	95	5
1e	0.024	3 (8, 15)	35 (13, 8)	100	0
1a	0	5	100[e]	19	81
1b	0	5	100[e]	19	81
1c	0	5	100[e]	40	60
1d	0	5	95	72	36
1e	0	5	73	83	17

[a] Solutions containing sodium acetate also contain 1% acetic acid. Solutions without sodium acetate contain about 2% acetic acid. [b] The per cent isoimide was determined at three different times: 3 min (time of total solution of the maleamic acid, a later time). The analysis at 3 min were carried out on the soluble portion of the reaction mixtures. [c] The per cent isoimide in the isoimide–imide product. [d] The amount of acetanilide could not be easily determined from the spectra. [e] Maximum amount of imide as determined by vpc was 10%.

Discussion

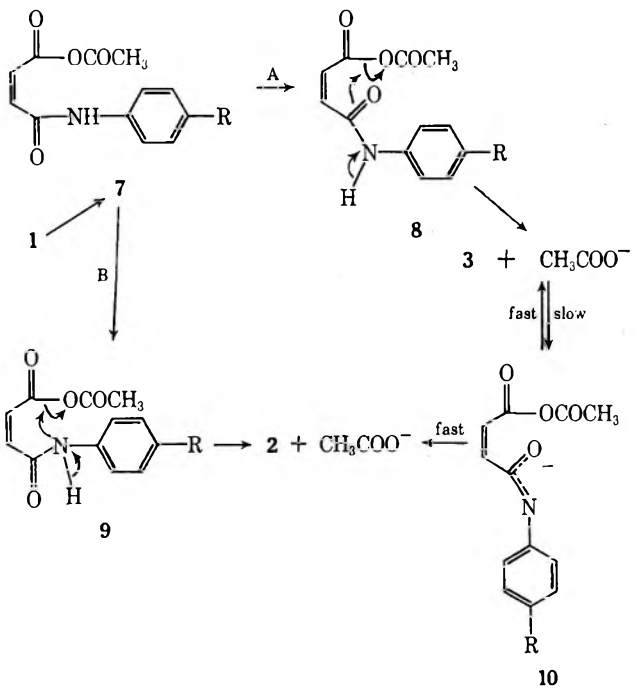
In contrast to the observations of Roderick on the dehydration of **5b**,[5] we have found that dehydrations of N-arylmaleamic acids (**1**) with acetic anhydride alone have given mixtures in which the maleisoimides predominate over the maleimides. In the presence of sodium acetate, more imide was formed initially and the ratio of maleimide to maleisoimide increased with decreasing electron density of the benzene ring. With the dehydration of **1e**, this ratio became greater than one. The rates of the rearrangement of the isoimides to the imides are not high enough to account for all of the imides produced in the presence of sodium acetate at 3 min. The acetic acid produced as the reaction proceeds would be expected to increase the rate of the rearrangement reaction and the possibility of catalysis by the other species present in the reaction cannot be

ruled out. In all the dehydrations reported here it is clear that the imides obtained when the reactions are run for longer periods[1,2] must be substantially derived from the isoimides by rearrangement.

The acetanilides isolated earlier by Kretov and Kul'chitskaya in the dehydrations of N-arylmaleamic acids at high temperatures with acetic anhydride were obtained along with maleic anhydride even at moderate temperatures. This "side reaction" is actually the main reaction in the dehydrations of **1a**, **1b**, and **1c** without sodium acetate.

The following reaction pathways may be suggested to account for these results. The first step in the dehydration reaction may be formation of the acetic acid–maleamic acid mixed anhydride **7**. This species could lose acetic acid in one of two ways (Scheme I). Path A

SCHEME I



involves participation by the neighboring amide carbonyl oxygen to eject acetate ion with simultaneous or subsequent loss of the proton on nitrogen to form the isoimide. Studies on the dehydration of amic acids with dicyclohexylcarbodiimide support a similar mechanism for these reactions,[11] and related mechanisms have been proposed for trifluoroacetic anhydride dehydrations.[5,6] The high ratio of isoimide to imide observed here may be the result of a large contribution to the structure of **7** from the amide dipolar resonance structure.[12] Hedaya, Hinman, and Theodoropulos have proposed that tautomerism of the amide may be involved in reactions leading to high isoimide yields.[6]

Path B involves loss of acetate ion assisted by the attack of nitrogen with simultaneous or subsequent loss of the proton on nitrogen to form the imide **2**.[13] Acetate ion probably hastens the formation of the mixed anhydride and it might aid in the loss of a proton from **8** and **9**.

The mechanism of the acetate-catalyzed isoimide–imide rearrangement reaction proposed previously[4,6] and supported by the kinetic studies of the rearrangement of **6a** to **4a**[8] is further supported by the results of the present work. That attack occurs at the carbonyl carbon seems probable because of the products obtained when isoimides are treated with other nucleophiles.[8,14] That ring closure to imide is not the slow step is supported by the increase in rate observed when R is an electron-withdrawing substituent. It is probable that some of the effect of substitution on the isoimides in the acetate-catalyzed rearrangement is due to stabilization of a transition state in which a considerable amount of negative charge has developed in that portion of the molecule which might be classified as the leaving group. The effect of substitution is similar to that observed in the nucleophile-catalyzed hydrolysis of phenyl esters.[15]

The effect of substitution in the ring attached to nitrogen for the acetate-catalyzed rearrangement of cyclic isoimides is opposite to the effect of substitution in the ring attached to nitrogen for the uncatalyzed rearrangement of acyclic isoimides.[7b] Curtin and Miller have proposed that this thermal reaction proceeds from isoimide to imide through a four-centered cyclic transition state, a route which is denied to the cyclic isoimides.

Maleic anhydride and the acetanilides may be formed directly from **7** by an internal attack of the nitrogen on the acetate carbonyl, but this process would involve a seven-membered ring transition state. It has been suggested that the heptafluorobutyranilide obtained from the reaction of heptafluorobutyric anhydride with N-phenylsuccinamic acid was formed by a similar mechanism.[14b] Alternatively, **7** could undergo a bicyclo[3.2.1] rearrangement analogous to those proposed by Newman and Courduvelis[16] with the formation of **10**. This intermediate could eliminate acetic acid to form isoimide **3** or collapse *via* a four-center mechanism to form acetanilide and maleic anhydride. In the absence of acetate ion, process C might become competitive with processs A and B (Scheme II).

Another possible route to the formation of maleic anhydride and the acetanilides is participation by neighboring carboxyl in loosening the amide carbon–nitrogen bond to the extent that the amine could be captured by acetic anhydride as shown in path D. A similar mechanism has been proposed for the hydrolysis of amides containing a neighboring carboxyl group.[8,17]

Mechanisms which involve starting with imides or isoimides are ruled out by the fact that no maleic anhydride or acetanilides are formed in the simple

(11) R. Paul and A. S. Kende, *J. Amer. Chem. Soc.*, **86**, 4162 (1964).

(12) J. D. Roberts and M. J. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1964, p 674.

(13) A related experiment on the succinamic–acetic acids mixed anhydride has been reported. The ring closure to imide has a Hammett ρ value of −1.649: R. C. Thamm, Ph.D. Thesis, University of Illinois, 1957; *Dissertation Abstr.*, **17**, 2428 (1957).

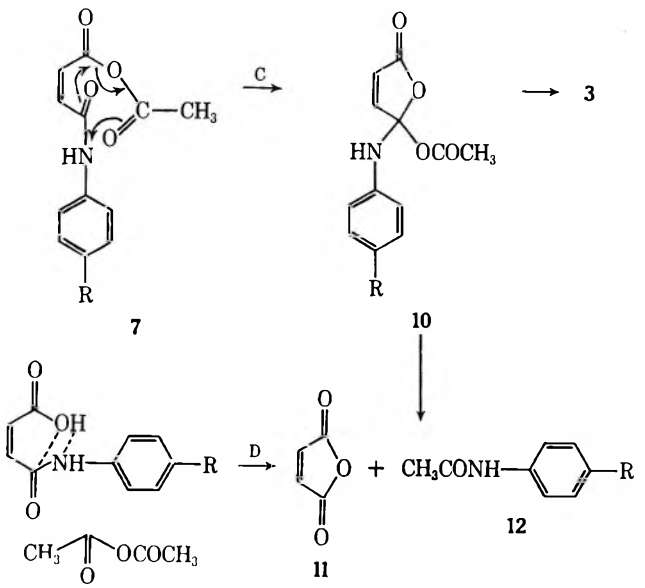
(14) (a) Y. L. Fan and D. F. Pollart, *J. Org. Chem.*, **33**, 4372 (1968); (b) W. R. Roderick and P. L. Bhatia, *ibid.*, **28**, 2018 (1963); (c) C. K. Sauers and R. J. Cotter, U. S. Patent 3,041,376 (1962); *Chem. Abstr.*, **58**, 4432(1963); (d) C. K. Sauers and R. J. Cotter, U. S. Patent 3,023,240 (1962); *Chem. Abstr.*, **57**, 11,100 (1962).

(15) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966, p 21.

(16) M. S. Newman and C. Courduvelis, *J. Amer. Chem. Soc.*, **88**, 781 (1966).

(17) (a) M. L. Bender, F. Chloupek, and M. C. Neveu, *ibid.*, **80**, 5380 (1958); (b) G. Dahlgren and N. L. Simmerman, *J. Phys. Chem.*, **69**, 3626 (1965); (c) H. Morawetz and J. Shafer, *J. Amer. Chem. Soc.*, **84**, 3783 (1962).

SCHEME II



rearrangement reactions. The present data do not permit a choice between paths C and D.[18]

Experimental Section

The microanalyses were performed by George Robertson, Florham Park, N. J. Melting points are uncorrected. Nuclear magnetic resonance spectra were obtained with a Varian A-60A spectrometer.

Maleisoimides.—The maleisoimides were prepared from the corresponding maleamic acids by dehydration with N,N'-dicyclohexylcarbodiimide.[4,19] Two maleisoimides were new compounds, **3d** and **3e**. N-*p*-Chlorophenylmaleisoimide (**3d**) was obtained in 90% yield by the dehydration of N-*p*-chlorophenylmaleamic acid with N,N'-dicyclohexylcarbodiimide. The product crystallized as yellow plates from ether, mp 96–98°. *Anal.* Calcd for $C_{10}H_6NO_2Cl$: C, 57.85; H, 2.91; N, 6.75. Found: C, 57.68; H, 2.88; N, 6.48. N-*p*-Acetylphenylmaleisoimide (**3e**) was obtained similarly in 75% yield. Pale yellow crystals isolated from ether–dichloromethane had mp 120.5–123°. *Anal.* Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.17. Found: C, 66.70; H, 4.34.

Rearrangement of N-Arylmaleisoimides to N-Arylmaleimides. Kinetic Studies.—Reagent grade acetic anhydride was distilled before use. A large forerun was discarded, then the fraction boiling at 136–138° was collected. Solutions of reagent grade fused sodium acetate and/or acetic acid were prepared from this material. The weighed maleisoimides were dissolved at room temperature in these solutions. The solutions were transferred to ten to twelve nuclear magnetic resonance tubes, capped with pressure caps, and placed in a constant-temperature bath. One tube was removed within 1 min and the time recorded as time zero. Subsequent tubes were removed until the reaction had proceeded to 70–90% conversion. After removal from the bath and before analysis the tubes were stored at 0°. Analysis was carried out by running the nuclear magnetic resonance spectra on an expanded scale (250–100-cps sweep width) followed by integration of the spectra. The value for the integral (average of two or more determinations of the integral) of the maleimide olefinic peaks was halved and the integral for the upfield maleisoimide olefinic peaks was recorded as read. The per cent isoimide was calculated from the following formula.

$$\% \text{ isoimide} = \frac{\text{isoimide upfield olefinic integral} \times 100}{\frac{1}{2}\text{ maleimide olefinic integral} + \text{isoimide upfield olefinic integral}}$$

This method gave good agreement (within 2%) in analyses of known N-*p*-tolylmaleisoimide-N-*p*-tolylmaleimide mixtures from 100 to 40% isoimide but was not so accurate below 40% isoimide or with the other isoimide–imide mixtures. It was possible to calibrate the method using solutions of known compositions for each isoimide–imide pair and thus to obtain a corrected per cent isoimide. When this was done the corrected per cent isoimide agreed with the weight per cent isoimide within 3%. First-order rate constants were calculated by computer using the integrated form of the rate equation and the method of least squares. The data presented in Table II are average values for k of two or more duplicate runs. Sodium acetate solutions made with acetic anhydride containing 1% acetic acid produced the same rate constants as those made from freshly distilled acetic anhydride with a prolonged reflux time to effect solution. Sodium acetate occasionally crystallized from the solutions on standing which indicates that the solutions are supersaturated at room temperature. It was necessary to warm the solutions, cool them to room temperature, and then remove the required amount of acetic anhydride containing the sodium acetate by pipet. Errors in concentration probably resulted from this procedure.

Product Studies.—The nuclear magnetic resonance tubes from a kinetic run were returned to the bath for 7–10 half-lives. The solutions were cooled, poured into saturated aqueous sodium bicarbonate solution, and stirred until the acetic anhydride had hydrolyzed. The maleimides were isolated by filtration, dried, and weighed. The yields were above 90% and the nuclear magnetic spectra of the acetic anhydride solutions corresponded to those of the authentic *para*-substituted N-phenylmaleimides.

Dehydrations of N-Arylmaleamic Acids. Composition of Products.—Samples of the maleamic acids (**1a–e**, 0.5 g) were added to 5 ml of prewarmed solutions of 0.024 M sodium acetate in acetic anhydride. These were placed in a bath at 75°. The yellow supernatant liquids were drawn off and analyzed by nmr at 3 min, at the time of total solution, and at later times. The relative amounts of the components of the mixture were estimated from the integrals of the olefinic peaks for maleic anhydride (at δ 7.19 relative to tetramethylsilane), the olefinic integrals for the maleimides, and the upfield maleisoimide olefinic peaks. The calibration used in the kinetic runs was used to calculate the isoimide–imide ratio. The reaction was repeated with acetic anhydride containing about 2% acetic acid. After 5 min the supernatant liquids were removed and analyzed. When freshly distilled acetic anhydride was used the reaction was very slow because of the low solubility of the acids, and the per cent of maleic anhydride formed from **1a**, **1b**, and **1c** was lower than when acetic acid was present. Some rearrangement of isoimide to imide occurred on vpc columns. This method was used to detect imide in the acetic anhydride alone dehydrations of **1a**, **1b**, and **1c**. The maximum amount of imide observed was 10%. The column used was 3% SE-30 on Aeropack 30 at 190°.

Isolation of Products. *p*-Methoxyacetanilide.—Maleamic acid **1a** (2 g) was added to 5 ml of acetic anhydride and the mixture contained in a test tube was heated in a boiling-water bath for 30 min. The nmr of the mixture indicated a large amount of maleic anhydride as well as the acetanilide and the isoimide. The reaction mixture was cooled and poured into saturated aqueous sodium bicarbonate solution to remove acetic anhydride. The crude product was recrystallized from water yielding 1.1 g (73%) of crystals, mp 124–126.5°. A mixture melting point with authentic[20] *p*-methoxyacetanilide was 126.5–128° (lit.[21] mp 127°).

***p*-Methylacetanilide and N-*p*-Tolylmaleisoimide.**—*p*-Methylacetanilide was isolated from the dehydration of **1b** at 100° followed by treatment of the reaction mixture with aqueous sodium

(18) Tracer studies would differentiate between paths C and the other mechanisms since only in C is one of the oxygens in the maleic anhydride derived from the solvent. We hope to do these experiments.

(19) Attempts to prepare N-*p*-nitrophenylmaleisoimide by the above method gave complex mixtures of products. The nuclear magnetic resonance spectrum of the mixture indicated some isoimide was present. Dehydration of the amic acid with ethyl chloroformate and triethylamine[4] produced the imide. Attempts to prepare the isoimide (which has been obtained previously by dehydration of the amic acid with trifluoroacetic anhydride[14b]) were discontinued when it became evident that its rearrangement rate would probably be too fast for convenient measurement.

(20) The authentic acetanilides were prepared following the directions in R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1964, p 259.

(21) M. Frankel and S. Patai, "Tables for Identification of Organic Compounds," 2nd ed, The Chemical Rubber Publishing Co., Cleveland, Ohio, 1964.

hydroxide solution. The yield after recrystallization from water was 76% crystals having mp 143–147°, mmp 144–147° (lit.[21] mp 147°). In another run the crude product was chromatographed in cyclohexane–benzene on Florisil. N-*p*-tolylmaleisoimide (5%) was isolated having mp 70–72° (lit.[14b] mp 74°).

N-Phenylmaleimide, N-Phenylmaleisoimide, and Acetanilide.—The dehydration reaction of 1c was carried out as described above. The crude product was dissolved in benzene and the solution was dried with magnesium sulfate. The dried benzene solution was chromatographed on Florisil and 12% N-phenylmaleisoimide and 11% N-phenylmaleimide were isolated. Nmr indicated that each compound was contaminated with about 10% of the other. Later fractions gave 35% acetanilide, mp 112–114°, mmp 112–115° (lit.[21] mp 114°).

N-*p*-Chlorophenylmaleimide and *p*-Chloroacetanilide.—The reaction was run as above and the crude mixture was poured into saturated sodium bicarbonate solution. The precipitate formed was dried in air and chromatographed on Florisil with cyclohexane–benzene to yield 33% N-*p*-chlorophenylmaleimide [mp 107–109°, mmp 107–109° (lit.[2] mp 108–110°)] and in a later fraction 37% *p*-chloroacetanilide, mp 176–177° (lit.[21] mp 179°).

N-*p*-Acetylmaleimide.—In a similar manner 40% N-*p*-acetylmaleimide was obtained, mp 152–155° (lit.[22] mp 151°).

***endo*-Norbornene-*cis*-5,6-dicarboxylic Acid Monomethyl Ester.**—A third run of the dehydration reaction of 1b in acetic anhydride alone was treated with excess cyclopentadiene.[23] After the exothermic reaction had subsided, an equal volume of methanol was added and the solution was heated at reflux for 2 hr. The solvents were removed by distillation and the residue was poured into water and extracted with ether. The ether extracts were combined and extracted with saturated sodium bicarbonate solution. The aqueous solution was acidified with concentrated hydrochloric acid to pH 3 and extracted with ether. After drying (magnesium sulfate) the ether was removed by evaporation. The residue, a clear colorless oil, solidified on standing to a white solid, mp 79–82° (lit.[24] mp for *endo*-norbornene-*cis*-5,6-dicarboxylic acid monomethyl ester, 76–78.5°). The nmr was identical with that of an authentic sample.

(22) B. Matkovics, L. Ferenezi, and Gy. Selneczi, *Acta Univ. Szgeded. Acta Phys. Chem.*, **4**, 134 (1958); *Chem. Abstr.*, **53**, 14934 (1959).

(23) L. F. Fieser, "Organic Experiments," D. C. Heath and Co., Boston, Mass., 1964, p 83.

(24) M. S. Morgan, R. S. Tipson, A. Lowy, and W. E. Baldwin, *J. Amer. Chem. Soc.*, **66**, 404 (1944).

Registry No.—**2a**, 1081-17-0; **2b**, 1631-28-3; **2c**, 941-69-5; **2d**, 1631-29-4; **2e**, 1082-85-5; **3a**, 19990-24-0; **3b**, 19990-25-1; **3c**, 19990-26-2; **3d**, 19990-27-3; **3e**, 19990-28-4; acetic anhydride, 108-24-7.

Acknowledgments.—I am indebted to The Society of Sigma Xi and The Rutgers Research Council for financial support of this work and to Professor Benjamin Carroll of the Rutgers Computer Center for assistance in obtaining the computer results. The Varian A-60A nuclear magnetic resonance spectrometer was purchased with the aid of a grant to the Chemistry Department of Douglass College from the National Science Foundation.

Stereochemistry of Microbiological Hydroxylation. II. Oxygenation of 1-Benzoylalkylpiperidines

ROY A. JOHNSON, HERBERT C. MURRAY, LESTER M. REINKE, AND GUNTHER S. FONKEN

The Upjohn Company, Kalamazoo, Michigan 49001

Received November 7, 1968

The microorganism *Sporotrichum sulfurescens* has been found to oxygenate a series of 1-benzoylalkylpiperidines. Oxygenation of 1-benzoyl-4-*n*-propylpiperidine (**2**) gives 1-benzoyl-4-(2-oxo)propylpiperidine (**3**); of 1-benzoyl-4-methylpiperidine (**4**) gives 1-benzoyl-4-hydroxymethylpiperidine (**5**) and 1-benzoyl-4-methyl-4-piperidinol (**6**); of (±)-1-benzoyl-3-methylpiperidine (**7**) gives 1-benzoyl-3-methyl-3-piperidinol (**8**) and (−)-1-benzoyl-3-methyl-4-piperidinol (**9**); of (±)-1-benzoyl-2-methylpiperidine (**12**) gives (2*S*,3*S*)-1-benzoyl-2-methyl-3-piperidinol (**13**), (2*R*,4*S*)-1-benzoyl-2-methyl-4-piperidinol (**14**), and (2*R*-)1-benzoyl-2-methyl-4-piperidinone (**16**); and of 1-benzoyl-*cis*-2,6-dimethylpiperidine (**32**) gives 1-benzoyl-*cis*-2,6-dimethyl-3-piperidinol (**33**). The substrates, 1-benzoyl-2-ethylpiperidine (**19**) and 1-benzoyl-2-*n*-propylpiperidine (**25**), also are oxygenated.

The hydroxylation of organic compounds by microbial enzyme systems is a valuable reaction for the introduction of functionality into a saturated molecule. Of additional interest is the fact that enzymatic reactions, when performed upon the substrate specific to the enzyme, generally are highly stereoselective. Enzymatic reactions upon foreign substrates may also be stereoselective in which case they are particularly valuable in synthesis. Stereoselectivity may be of two types in the case of hydroxylation reactions. First, the introduction of a hydroxyl group in the place of a particular hydrogen atom in the substrate molecule may result in the formation of a single alcohol epimer. As examples, the hydroxylation of steroids usually gives either the α- or the β-hydroxy product rather than a mixture of the two.[1] The second potential result, which is a consequence of the first, is the formation of an optically active product, either through the introduction of asymmetry into the molecule or through resolution of a racemate.[2] Examples in which both hydroxylation and introduction of optical activity occur are few, largely because most substrates used for this reaction have been naturally occurring steroids. Two notable exceptions are the hydroxylation and resolution of a racemic intermediate by the mold *Ophiobolus herpotrichus* in the total synthesis of *d*-aldosterone[3] and of a series of synthetic gonanes by the microorganism *Aspergillus ochraceus*.[4]

We have recently described the microbial hydroxylation of molecules other than steroids by the microorganism *Sporotrichum sulfurescens* in which both the stereospecific introduction of hydroxyl[5] and the intro-

(1) *Cf.* C. Tamm, *Angew. Chem. Intern. Ed. Engl.*, **1**, 178 (1962).

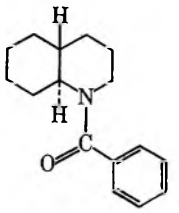
(2) Resolution may be accomplished upon either the substrate or the product. Resolution of the latter requires further degradation of one enantiomer of the product.

(3) E. Vischer, J. Schmidlin, and A. Wettstein, *Experientia*, **12**, 50 (1956).

(4) L. L. Smith, G. Greenspan, R. Rees, and T. Foell, *J. Amer. Chem. Soc.*, **88**, 3120 (1966).

(5) (a) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968); (b) R. A. Johnson, M. E. Herr, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3195 (1968); (c) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3201 (1968); (d) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3207 (1968).

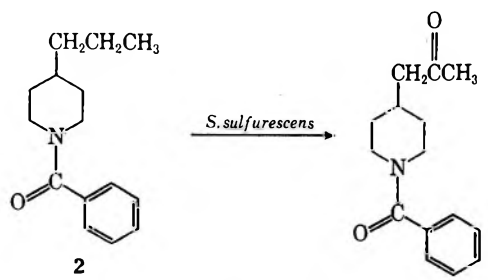
duction of optical activity were observed.[5a,b] Of particular interest was the hydroxylation of (±)-1-benzoyl-*trans*-decahydroquinoline (**1**). We have also



1

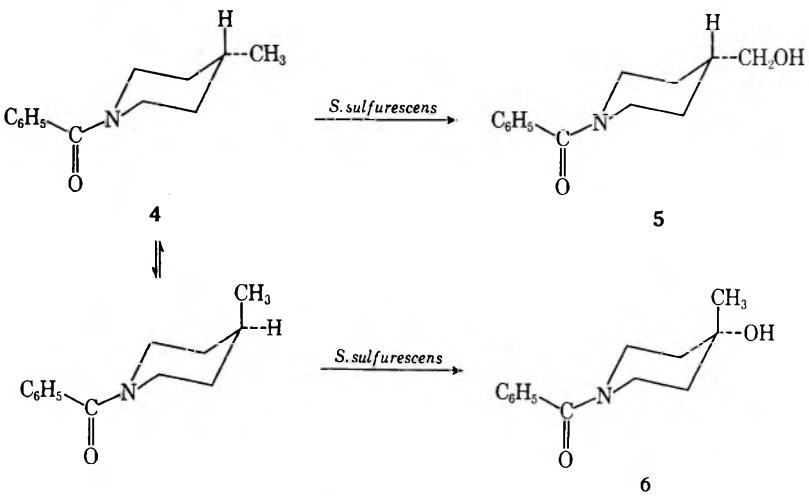
observed[6a] that 1-benzoylpiperidine is hydroxylated at the 4 position, whereas the piperidine ring contained in the nucleus of **1** is not hydroxylated. It became of interest therefore to investigate the microbial hydroxylation of a series of 1-benzoyl-*x*-alkyl-substituted piperidines to determine (1) if these compounds could be hydroxylated, (2) if hydroxylation might occur in the alkyl protions of the molecules, and (3) if stereoselectivity, with respect to both introduction of the hydroxyl group and introduction of optical activity, would be observed in these molecules. In the following discussion, the successful hydroxylation of such a series of substrates is described and structural and stereochemical assignments are made on the basis of the spectral data of the hydroxylated products and their ketonic oxidation derivatives.

1-Benzoyl-4-*n*-propylpiperidine (**2**) was the first compound in this series used as a substrate for the hydroxylation reaction with *Sporotrichum sulfurescens*. A single oxygenated product (**3**) was obtained and was shown to be a ketone by its infrared spectrum. The product was easily identified as 1-benzoyl-4-(2-oxo)-propylpiperidine (**3**) by examination of its nmr spectrum, which had a doublet at 146 Hz and a singlet at 127 Hz corresponding to the methylene and methyl groups adjacent to the carbonyl group, respectively. The formation of **3**, which very recently has been prepared by chemical synthesis,[7] is noteworthy in several respects. First it provides an as yet unusual example of hydroxylation in an acyclic portion of a molecule by *S. sulfurescens*. Secondly, it is the only example of a major ketonic product obtained in the present series of substrates and as such is in agreement with the notion of further oxidation of conformationally mobile substrates, which has been outlined previously.[6]



2

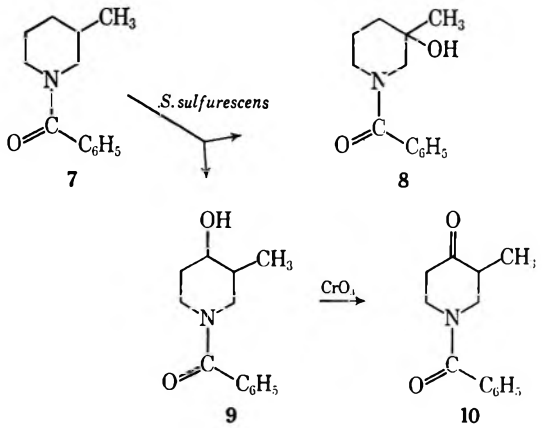
Hydroxylation of 1-benzoyl-4-methylpiperidine (**4**) with *S. sulfurescens* gave two hydroxylated products. These were readily identified by their nmr spectra as 1-benzoyl-4-methyl-4-piperidinol (**6**) and 1-benzoyl-4-hydroxymethylpiperidine (**5**), the 4-methyl group of the former appearing as a singlet at 72 Hz and the 4-methylene group of the latter as a doublet at 203 Hz (J = 5 Hz). While the exact reaction paths leading to products **5** and **6** cannot easily be determined, we suggest the possibility that **5** arises through hydroxylation of the conformer of **4** having the equatorial methyl group and **6** from hydroxylation of the conformer of **4** having the axial methyl group. Such a pathway to **6** is consistent with the observation that in rigid systems the hydroxyl group is introduced in a *trans* orientation with respect to the amide functional group,[6] assuming that the benzoyl function occupies predominately an equatorial configuration in the present case.



When (±)-1-benzoyl-3-methylpiperidine (**7**) was used as a substrate, two hydroxylated compounds (**8** and **9**) were obtained as the products. The first alcohol obtained from chromatography of the products was readily identified as the tertiary alcohol, 1-benzoyl-3-methyl-3-piperidinol (**8**). The nmr spectrum of **8** contained a singlet at 69 Hz for the uncoupled tertiary methyl group at C-3. In addition, the axial proton at C-2 was a sharp doublet as a result of being coupled only with the geminal C-2 equatorial hydrogen. The second alcohol (**9**) could be oxidized to a ketone (**10**) with chromic acid. Only positions C-4 and C-5 of the 3-methylpiperidine nucleus can accommodate a ketone carbonyl group and, from the lack of a characteristic nmr signal attributable to a methylene group isolated at C-6 by a C-5 carbonyl, the position of the oxygen in

(6) (a) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3187 (1968); (b) *ibid.*, **33**, 3217 (1968).

(7) R. J. Sundberg, *ibid.*, **33**, 487 (1968).



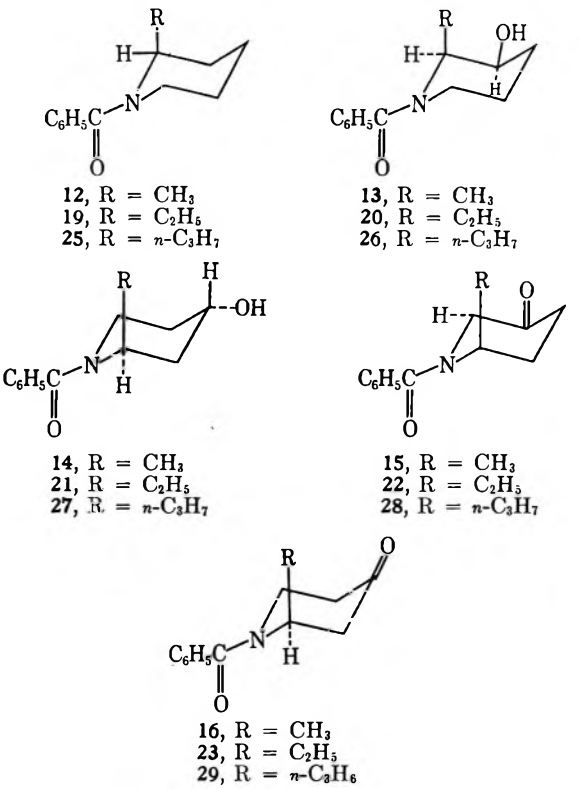
7 8 9 10

ketone **10**, and therefore in alcohol **9**, is assigned to C-4. The configuration of the C-4 hydroxyl group in **9** can be assigned on the basis of the nmr spectrum of the trichloroacetylurethan derivative (**11**) of **9**. The splitting of the C-4 signal, now shifted downfield, by two adjacent axial protons and one adjacent equatorial proton is consistent with an assignment of an axial configuration to the C-4 proton. The configuration of the hydroxyl group is therefore equatorial.

It now was necessary to consider the question of optical activity in this series of compounds since substrate **7** contains an asymmetric carbon and a second such center has been introduced in the formation of product **9**. The crystalline alcohol **9** was optically active ($[\alpha]_D$ −21°) but the crystalline alcohol **8** was optically inactive at the sodium D line. The lack of optical activity in **8** may be due to the fact that only the racemate was obtained in crystalline form in this case, since the amount of crystalline material (7% yield) obtained was only a small part of the crude fraction of **8**. Similarly, crystalline **9** (6% yield) may represent the preferential crystallization of the enantiomer.

The homologous series of 2-methyl-, 2-ethyl-, and 2-*n*-propyl-substituted piperidine substrates was submitted to the microbial oxygenation reaction and similar products were obtained from each. In considering the hydroxylation of these substrates as well as the structures of the products, it should be pointed out that the preferred conformation of these substrate molecules is the one in which the 2-alkyl group is in an axial configuration.[8] Similarly, the methyl groups in the substrate 1-benzoyl-2,6-dimethylpiperidine, discussed later below, also are found in axial configurations.[8]

Three products, two major and one minor in terms of quantity, were isolated from the oxygenation of (±)-1-benzoyl-2-methylpiperidine (**12**). Obtained in largest quantity was a hydroxylated product (**14**), whose chromic acid oxidation product (**16**) was identical with the minor reaction product. The position of the ketone group in **16** was determined to be at C-4, since in its nmr spectrum (see Experimental Section) the C-2 proton and the C-6 protons all are split by the protons of adjacent saturated carbons, *i.e.*, C-3 and C-5. The hydroxyl group of **14** therefore is also at C-4 and it is assigned an equatorial configuration on the basis of the splitting of the C-4 proton in the nmr spectrum of the trichloroacetylurethan derivative (**17**).



12, R = CH_3
19, R = C_2H_5
25, R = *n*-C_3H_7

13, R = CH_3
20, R = C_2H_5
26, R = *n*-C_3H_7

14, R = CH_3
21, R = C_2H_5
27, R = *n*-C_3H_7

15, R = CH_3
22, R = C_2H_5
28, R = *n*-C_3H_7

16, R = CH_3
23, R = C_2H_5
29, R = *n*-C_3H_6

The second major product, alcohol **13**, obtained in the oxygenation of **12**, also had a secondary hydroxyl group, which was oxidized to a ketone (**15**). The ketone carbonyl may be at C-3 or at C-5 in **15**. Again, the nmr spectrum of the ketone allows assignment of structure to this compound. The C-2 proton signal is found as a quartet (J = 7 Hz) at 290 Hz in the spectrum of **15**, indicating that it is being split only by the protons of the axial C-2 methyl group. The ketone group must therefore be placed at the C-3 position to account for the lack of further splitting of the C-2 proton. The hydroxyl group of **13**, therefore also at C-3, is assigned an equatorial configuration by analogy with the similar 1-benzoyl-2-ethyl-3-piperidinol (**20**) obtained by hydroxylation of the 2-ethylpiperidine substrate and discussed below. The nmr spectra of the two alcohols, **13** and **20**, and their trichloroacetylurethan derivatives, **18** and **24**, are very similar between 100 and 300 Hz; however, only in the spectrum of **24** is the C-3 proton shifted downfield sufficiently to allow assignment of an axial configuration (half band width = 19 cps)[9] and therefore an equatorial configuration to the hydroxyl group. The question of optical activity in these products is discussed below.

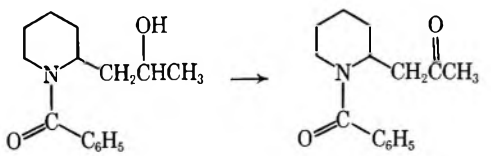
Oxygenation of (±)-1-benzoyl-2-ethylpiperidine (**19**) gave two hydroxylated products. Purification of these by chromatography gave first a compound (**20**) analogous to the C-3 hydroxylated product **13**, as discussed above, which was oxidized by Jones reagent to a ketone (**22**). The similarity of the nmr spectrum of **22** to the spectrum of **15** (see Experimental Section) is convincing evidence that the ketone carbonyl in **22** is also at C-3. The assignment of an equatorial configuration to the hydroxyl group at C-3 in **20** was

(8) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968); also Y. L. Chow, C. J. Colon, and J. N. S. Tam, *Can. J. Chem.*, **46**, 2821 (1968); H. Paulsen, K. Todt, and H. Ripperger, *Chem. Ber.*, **101**, 3365 (1968); F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(9) *Cf.* R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

discussed above. The second product **21** was also oxidized by Jones reagent to a ketone (**23**). Both had nmr spectra very similar to the 4-hydroxy and 4-keto products in the 2-methyl series and therefore are assigned the analogous structures.

Oxygenation of the third member of the 2-alkyl series, 1-benzoyl-2-*n*-propylpiperidine (**25**), gave a mixture of three oxygenated products. Two of these (**26** and **27**) are similar to compounds **13** and **14**, derived from the 2-methylpiperidine substrate, and are assigned the analogous structures. The third product (**30**) has a hydroxyl group at the 2′ position of the *n*-propyl side chain as shown by the nmr spectra of it and of the ketone **31** obtained from it after oxidation. The



30 **31**

presence of a signal for the methyl group in the spectrum of **30** as a doublet (J = 6 Hz) at 74 Hz and as a singlet at 131 Hz in the spectrum of **31** requires this assignment of structure. Formation of compound **30** and oxidation to **31** represent a microbial synthesis of the N-benzoyl derivatives of the alkaloids sedridine and isopelletierine, respectively.

Several points of similarity of the products from the above homologous series of substrates should be noted. First, the two major products isolated from each bioconversion are a 3-hydroxy and a 4-hydroxy compound in which the configuration of the hydroxyl group is equatorial in each case. This configuration places the hydroxyl groups nearest to a 1,3- or a 1,4-diequatorial relationship that is possible in these molecules and is consistent with the previously observed *trans* relationship between the hydroxyl group and the electron-rich benzamide group in microbial hydroxylation products. Secondly, a similarity of the products can be seen in their optical activities, which are summarized in Table I. These results suggest that

TABLE I

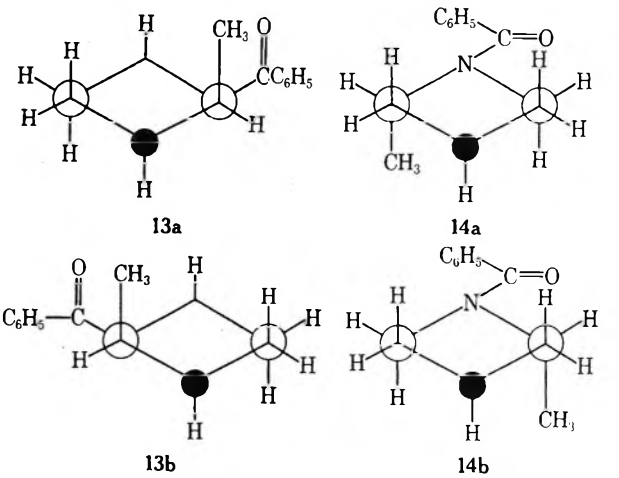
SPECIFIC ROTATIONS OF OXYGENATED 1-BENZOYL-2-ALKYLPIPERIDINES

Alkyl derivative	[α]D, deg 3-OH	4-OH	3 C=O	4 C=O
2-Methyl	+35	−29	+74	−19
2-Ethyl	+51	−22[a]	+50	
2-*n*-Propyl	+51	−26[a]		

[a] Measured on filtrates of crystalline, optically inactive analytical samples.

analogous reaction pathways are followed in the hydroxylation of each substrate. The formation of optically active products from these racemic substrates may result from either the preferential hydroxylation of one enantiomer of the substrate at a single position or the further preferential metabolism (and loss) of one enantiomer of the product molecules. In other experiments similar to these the total yield of optically active products exceeded 50%, which can best be interpreted as preferential hydroxylation of the enantiomers of the substrate at different positions. It seems probable that this is the case with the present substrates as well.

The availability of a method for the resolution of 2-methylpiperidine[10] and knowledge of the absolute configuration of (2*S*)-(+)-2-methylpiperidine[11] and its conversion to (2*S*)-(+)-1-benzoyl-2-methylpiperidine[12] enabled us to determine the absolute configuration of the optically active products **13** and **14**. A sample of (2*S*)-(+)-1-benzoyl-2-methylpiperidine ([α]D +38°, lit.[12] +41°) was prepared and used as a substrate with *S. sulfurescens*. Before examining the reaction product, an attempt was made to predict the structures of **13** and **14** with the use of a spatial orientation model, outlined previously.[6b] Four structures are possible for these products, two arising from each enantiomer of the substrate. These four structures appear as shown in the following projection formulas when oriented as defined previously.[6b]



13a **14a**

13b **14b**

Hydroxylation at C-3 of the *S* form of the substrate would give **13a**, whereas hydroxylation of the *R* form at C-3 would give **13b**. Likewise, hydroxylation at C-4 of the *S* form would give **14a** while hydroxylation of the *R* form at C-4 would give **14b**. From previous examples, a preference for an orientation of unsymmetrical molecules having the bulk of the molecule in the upper right rear octant was observed.[6b] In the present examples such preference predicts that hydroxylation of the *S* form of the substrate will give **13a** as the major product. Indeed, the major product isolated from hydroxylation of (2*S*)-1-benzoyl-2-methylpiperidine with *S. sulfurescens* was **13a**, identical with compound **13** isolated from bioconversion of racemate **12**. It can be expected that hydroxylation of the *R* form of the substrate would give **14b** as the product. The methyl group of structure **14b** is seen to lie slightly in the lower right octant, suggesting that this area of space is available to substrate molecule when in contact with the hydroxylating enzyme.

Finally, oxygenation of 1-benzoyl-*cis*-2,6-dimethylpiperidine (**32**) gave a single major product (**33**, [α]D −5°). The optical activity of **33** shows that it cannot be symmetrical (*i.e.*, a 4-hydroxy derivative) and the secondary character of the hydroxyl group, shown by oxidation to a ketone, leaves only C-3 as the position

(10) W. Marckwald, *Chem. Ber.*, **29**, 43 (1896).
(11) H. Ripperger and K. Schreiber, *Tetrahedron*, **21**, 1485 (1965).
(12) O. Cervinka, A. Fabryova, and V. Novak, *Collect. Czech. Chem. Commun.*, **30**, 1742 (1965).

of hydroxylation in this product. Compound **33** could not be obtained as a sharp-melting solid; yet it was found homogeneous by tlc, vpc, and paper chromatography. This leads us to conclude that the product is optically impure, having an excess of the (−) enantiomer present as indicated by its optical rotation. A minor product (**34**) from this bioconversion had the empirical formula $C_{14}H_{19}NO_2$ suggesting that it was a dihydroxylated product. We were unable to obtain a satisfactory nmr spectrum of this material owing to its insolubility in the usual solvents.

Experimental Section[13]

Biotransformation Process.—The culture used in these experiments was *Sporotrichum sulfurescens* V. Beyma (ATCC 7159). The biotransformation procedure has been described previously,[6a] the only variation being that the dispersing agent Ultrawet DS-30 (2.5 ml/l.) was added to the fermentations.

Isolation of Products from the Microbiological Oxygenations.—The following general procedure was followed in the separation of the oxygenated products. The methylene chloride extracts of the fermentation beers were allowed to evaporate to dryness. The residues were redissolved in methylene chloride and chromatographed on Florisil (ratio of substrate to adsorbent 1:100) chromatography columns which were dry packed in Skellysolve B. Elution of the column with increasing proportions of acetone in Skellysolve B generally resulted in removal of the products in the range of 10–25% (v/v) acetone in Skellysolve B. Purity of the fractions could be determined by tlc on silica gel plates developed in 20% methanol–benzene with detection by uv, Dragendorff reagent, or iodine vapor. The appropriate fractions were combined in acetone and usually decolorized with activated charcoal. The products were then crystallized from acetone–Skellysolve B, unless indicated otherwise. The products from each substrate are described in the order in which they were eluted from the column.

Oxygenation of 1-Benzoyl-4-*n*-propylpiperidine (2).—Oxygenation of 2 (25.0 g, 0.108 mole) gave an oil product which was distilled (bp 168–172°, 0.15 mm), giving 7.91 g (0.0323 mole, 30%) of 1-benzoyl-4-(2-oxo)propylpiperidine (**3**). The distillate crystallized after standing 8 months giving colorless crystals, mp 69–71°. Two recrystallizations gave an analytical sample of **3**: mp 69–71°, lit.[7] mp 63–65°; $\nu_{C=O}$ 1715, 1630, $\nu_{C=C}$ 1600, 1575, 1525, 1495, ν_{Ph} 790, 735, 710 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$), 247 (2- and 6-H_{eq}, broad, 2 H), 174 (2- and 6-H_{ax}, broad triplet, J_{gem} = 13 Hz, 2 H), 146 (CH_2CO, doublet, J = 5 Hz, 2 H), 127 (CH_3, singlet, 3 H).

Oxygenation of 1-benzoyl-4-methylpiperidine (4) (25.0 g, 0.123 mole) gave a total of 18.6 g of crude oxygenated product. Two crops of **1-benzoyl-4-methyl-4-piperidinol (6)**, 1.342 g, mp 105–110°, and 2.239 g, mp 93–106° (total 16.3 mmoles, 13%), were obtained. Two recrystallizations gave an analytical sample of **6** as colorless crystals: mp 109–111°; ν_{OH} 3320, $\nu_{C=O,C=C}$ 1605, 1575, 1500, ν_{Ph} 785, 710 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$), 260–184 (2- and 6-H, 4 H), 108–82 (3- and 5-H, 4 H), 72 (CH_3, singlet, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.24; H, 7.77; N, 6.53.

Two crops of **1-benzoyl-4-hydroxymethylpiperidine (5)**, 4.721 g, mp 90–94°, and 1.557 g, mp 88–94° (total 28.6 mmoles, 23%), were obtained. Two recrystallizations gave an analytical sample of **5** as colorless crystals: mp 92–95°; ν_{OH} 3440, $\nu_{C=O,C=C}$ 1630, 1615, 1600, 1575, 1495, ν_{Ph} 800, 725, 715 cm^{-1} in Nujol; nmr (in Hz 60°, $CDCl_3$), 251 (2- and 6-H_{eq}, broad doublet, J_{gem} = 13 Hz, 2 H), 203 (CH_2O, doublet, J = 5 Hz, 2 H), 172 (2- and 6-H_{ax}, six-line pattern, J_{gem} = 13 Hz, 2 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.37; H, 7.94; N, 6.43.

Oxygenation of (±)-1-benzoyl-3-methylpiperidine (7) (25.0 g, 0.123 mole) gave, following chromatography, a crude weight of 15.6 g of oxygenation products. Two crops of **1-benzoyl-3-methyl-3-piperidinol (8)**, 1.350 g, mp 91–3°, and 0.415 g (total 8.10 mmoles, 7%), were obtained. Two recrystallizations gave an analytical sample of **8**: mp 92–94°; $[\alpha]_D$ 0° (chloroform); ν_{OH} 3410, $\nu_{C=O}$ 1605, $\nu_{C=C}$ 1580, 1505, ν_{Ph} 790, 740, 730, 700 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$) 225 (2- and 6-H_{eq}, doublet, J_{gem} = 13 Hz, 2 H), ~188 (6-H_{ax}, multiplet, 1 H), 184 (2-H_{ax}, doublet, J_{gem} = 13 Hz, 1 H), 69 (CH_3, singlet, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.12; H, 8.12; N, 6.59.

(−)-1-Benzoyl-3-methyl-4-piperidinol (9) was obtained as colorless crystals, mp 119–135°, 1.762 g (8.04 moles, 6%). Three recrystallizations gave an analytical sample of **9**: mp 141–143°; $[\alpha]_D$ −21° (c 0.628, chloroform); ν_{OH} 3330, $\nu_{C=O}$ 1610, $\nu_{C=C}$ 1575, 1530, 1495, ν_{Ph} 795, 745, 720, 705 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 242 (2- and 6-H_{eq}, broad singlet, 2 H), 210–158 (2- and 6-H_{ax}, multiple signals, 2 H), 56 (CH_3, doublet, J = 6 Hz, 3 H); trichloroacetylurethan derivative (**11**) of **9** nmr (in Hz, 60°, $CDCl_3$) 285 (4-H, triplet of doublets, J_{aa} = 8.5, J_{ae} = 4 Hz, 1 H), 242 (2- and 6-H_{eq}, doublet, J = 13 Hz, 1 H), 209–155 (2- and 6-H_{aa}, multiple signals, 1 H), 58 (CH_3, doublet, J = 6 Hz, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.24; H, 7.95; N, 6.39.

Oxidation of 9 with Jones reagent[14] gave ketone **10** as a viscous oil which failed to crystallize: nmr (in Hz, 37°, $CDCl_3$) 263 (2- and 6-H_{eq}, broad doublet, J = 13 Hz, 2 H), 222–180 (2- and 6-H_{ax}, multiple signals, 2 H), 174–140 (3- and 5-H, multiple signals, 3 H), 62 (CH_3, doublet, J = 6 Hz, 3 H).

Oxygenation of (±)-1-benzoyl-2-methylpiperidine (12) (25.0 g, 0.123 mole) gave a crude weight of 16.5 g of oxygenated products. A first crop, 0.252 g, and second crop, 0.061 g (1.44 mmoles, 1%), of **(2*R*)-1-benzoyl-2-methyl-4-piperidone (16)**, mp 111–116°, was obtained. Two recrystallizations gave an analytical sample of **16**: mp 117–118°; $\nu_{C=O}$ 1715, 1700, 1620, ν_{Ph} 790, 740, 700 cm^{-1} in Nujol; nmr (in Hz, $CDCl_3$) 298 (2-H, quartet, J_{CH_3} = 7 Hz, 1 H), 265 (6-H_{eq}, doublet, J_{gem} = 14 Hz, 1 H), 204 (6-H_{ax}, eight-line pattern, 1 H), 175–123 ($COCH_2$, multiple signals, 4 H), 75 (CH_3, doublet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.21; H, 7.07; N, 6.46.

Two crops, 1.225 g, mp 125–130°, and 1.533 g, mp 120–125° (total 12.6 mmoles, 10%), of **(2*S*,3*S*)-1-benzoyl-2-methyl-3-piperidinol (13)** were obtained. Two recrystallizations gave an analytical sample of **13**: mp 127–129°; $[\alpha]_D$ +35° (c 0.864, $CHCl_3$); ν_{OH} 3380, $\nu_{C=O}$ 1605, $\nu_{C=C}$ 1575, 1500, ν_{Ph} 745, 715, 705 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$) 268 (2-H, multiplet, 1 H), 234 (6-H_{eq}, doublet, J = 13 Hz, 1 H), 171 (6-H_{ax}, six-line pattern, 1 H), 67 (CH_3, doublet, J = 6 Hz, 3 H); trichloroacetylurethan derivative (**18**) of **13** nmr (in Hz, 60°, $CDCl_3$) 291 (2-H and –OCH, multiplet, 2 H), 241 (6-H_{eq}, doublet, J = 13 Hz, 1 H), 179 (6-H_{ax}, six-line pattern, 1 H), 75 (CH_3, doublet J = 6.5 Hz, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.26; H, 8.00; N, 6.68.

Two crops 4.277 g, mp 127–130°, and 1.303 g, mp 110–120° (total 25.5 mmoles, 21%), of **(2*R*,4*S*)-1-benzoyl-2-methyl-4-piperidinol (14)** were obtained. Two recrystallizations gave an analytical sample of **14**: mp 128–130°; $[\alpha]_D$ −29° (c 0.365, $CHCl_3$); ν_{OH} 3340, $\nu_{C=O}$ 1605, $\nu_{C=C}$ 1595, 1575, 1530, 1495, ν_{Ph} 795, 740, 715 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$) 274 (2-H, broad, 1 H), ~242 (6-H_{eq}, doublet, $J \simeq 13$ Hz, 1 H), 236 (4-H, seven-line pattern, $J_{aa} \simeq 11$ Hz, $J_{ae} \simeq 5.5$ Hz, 1 H), 178 (6-H_{ax}, triplet of doublets, J_{gem} = 13 Hz, J_{aa} = 3 Hz, 1 H), 72 (CH_3, doublet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.25; H, 7.83; N, 6.65.

Ketone **16** was also obtained when **14** was oxidized with chromic acid[13] in acetone. Recrystallization from acetone–Skellysolve B gave colorless crystals, mp 116–119°, $[\alpha]_D$ −19° (c 0.651, $CHCl_3$); the infrared spectrum in Nujol is identical with the spectrum of ketone **16** obtained above.

(2*S*)-1-Benzoyl-2-methyl-3-piperidone (15).—Oxidation of **13**

(13) Melting points were determined on a Fisher-Johns hot stage and are corrected. Magnesium sulfate was used as the drying agent. Infrared spectra were determined with either a Perkin-Elmer Infracord or Model 421 spectrophotometer. Ultraviolet spectra were determined on a Cary 14 spectrophotometer. The nmr spectra were determined at 60 Mc with a Varian Model A-60A spectrometer, using tetramethylsilane as an internal standard. Trichloroacetylurethan derivatives for determination of nmr spectra were prepared by the addition of a slight excess of trichloroacetyl isocyanate to the deuteriochloroform solution of the alcohol in the nmr sample tube.

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(0.352 g, 1.60 mmoles) with chromic acid in acetone gave 0.214 g (0.986 mmole, 62%) of crystalline ketone, mp 102–104°. Recrystallization from acetone–Skellysolve B gave colorless plates of **15**: mp 103–105°; $[\alpha]_D$ +74° (*c* 0.657, $CHCl_3$); $\nu_{C=O}$ 1715, 1620, $\nu_{C=C}$ 1600, 1575, 1495, ν_{Ph} 795, 730, 725 cm^{-1} in Nujol; nmr (in Hz, $CDCl_3$) 290 (2-H, quartet, J_{CH_3} = 7 Hz, 1 H), 248 (6-H_{eq}, doublet of triplets, J_{gem} = 14 Hz, $J_{}$ = 4 Hz, 1 H), 197 (6-H_{ax}, five-line pattern, J_{gem} = 14 Hz, J_{aa} = 7 Hz, J_{ae} = 7 Hz, 1 H), 155 (4-H, triplet J = 7 Hz, 1 H), 154 (4-H, triplet, J = 6 Hz, 1 H), 121 (5-H, quintuplet, $J \simeq 6$ Hz, 2 H), 84 (CH_3, doublet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.99; H, 7.09; N, 6.25.

Oxygenation of (2*S*)-1-Benzoyl-2-methylpiperidine.—The methylene chloride extract from the oxygenation of 2*S*-1-benzoyl-2-methylpiperidine (2.0 g, 0.00985 mole) was chromatographed on Florisil. A total of 0.778 g (0.00355 mole, 36%) of colorless crystals, mp 125–127, was obtained from crystallization from acetone–Skellysolve B. Two recrystalizations from acetone–Skellysolve B gave colorless crystals of (2*S*,3*S*)-1-benzoyl-2-methyl-3-piperidinol, mp 129–131°, $[\alpha]_D$ + 37° (c 0.608, chloroform), infrared spectrum in Nujol identical with the spectrum of **13** above.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.32; H, 7.67; N, 6.27.

Oxygenation of (±)-1-benzoyl-2-ethylpiperidine (19) (25.0 g, 0.115 mole) gave a crude weight of 17.0 g of oxygenated products. (+)-1-Benzoyl-2-ethyl-3-piperidinol (**20**) was obtained as an oil, which crystallized after long standing (8 months). Colorless crystals (5.399 g, 0.0232 mole, 20%), mp 109–111° were obtained. Two recrystallizations gave an analytical sample of **20**: mp 111–113°; $[\alpha]_D$ +51° (*c* 0.564, chloroform); ν_{OH} 3390, 3320, $\nu_{C=O,C=C}$ 1625 s, 1610 s, 1600, 1575, 1495 cm^{-1} in Nujol; nmr (in Hz, 60°, $CDCl_3$) 261 (2-H, broad singlet, 1 H), 247–210 (6-H_{eq}, 3-H, OH, 3 H), 167 (6-H_{ax}, six-line pattern, J_{gem} = 13 Hz, 1 H), 51 (CH_3, triplet, J = 7 Hz, 3 H); trichloroacetylurethan derivative (**24**) of **20** nmr (in Hz, 60°, $CDCl_3$) 299 (3-H, six-line pattern with ~5.5-Hz peak separation, 1 H), 276 (2-H, broad singlet, 1 H), 241 (6-H_{eq}, doublet, J_{gem} = 13 Hz, 1 H), 173 (6-H_{ax} six-line pattern, J_{gem} = 13 Hz, 1 H), 53 (CH_3, triplet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.25; H, 8.43; N, 6.06.

Three crops of crystalline **1-benzoyl-2-ethyl-4-piperidinol (21)**, 2.049 g (8.79 mmoles, 8%), mp 104–106°, were obtained. Two recrystallizations of the first crop gave an analytical sample of **23**: mp 107–109°, $[\alpha]_D$ 0°; ν_{OH} 3330, $\nu_{C=O,C=C}$ 1605 s, 1600 s, 1575, 1520, 1495, ν_{Ph} 790, 730, 705 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 234 (4-H, seven-line pattern, 1 H), 175 (6-H_{ax}, broad triplet, $J_{gem,aa}$ = 13 Hz, 1 H), 50 (CH_3, triplet, J = 7 Hz 3 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.06; H, 8.39; N, 6.03.

The third crop of **21** had $[\alpha]_D$ −22° (chloroform).

Oxidation of 20 with Jones reagent gave (+)-1-benzoyl-2-ethyl-3-piperidone (**22**) as colorless crystals, mp 61–63°, following three recrystallizations from acetone–Skellysolve B: $[\alpha]_D$ +50° (*c* 0.637, chloroform); $\nu_{C=O}$ 1720, 1615, $\nu_{C=C}$ 1600, 1575, 1495, ν_{Ph} 795, 725, 705 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 284 (2-H, broad, 1 H), 245 (6-H_{eq}, broad, 1 H), 197 (6-H_{ax}, five-line pattern, J_{gem} = 14 Hz, J_{ae} = 7 Hz, J_{aa} = 7 Hz, 1 H), 153 (4-H, triplet, J = Hz, 1 H), 152 (4-H, triplet, J = 6 Hz, 1 H), 118 (5-H, quintuplet, $J \simeq 7$ Hz, 2 H), 54 (CH_3, triplet, J = 7 Hz, 3 H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.73; H, 7.33; N, 5.91.

Oxidation of 21 with Jones reagent gave ketone **23** as a viscous oil: nmr (in Hz, 37°, $CDCl_3$) 274 (2-H, broad, 1 H), 264 (6-H_{eq}, doublet, J = 13 Hz, 1 H), 210–130 (6-H_{ax}, 3- and 5-H, multiple line, 5 H), 95 (ethyl CH_2, quintuplet, J = 7 Hz, 2 H), 54 (CH_3, triplet, J = 7 Hz, 3 H).

Oxygenation of (±)-1-benzoyl-2-*n*-propylpiperidine (25) (25.0 g, 0.108 mole) gave fractions as shown in Table II when the Florisil column was eluted with 20% acetone–Skellysolve B. Crystals in fraction 8 were washed with ether–Skellysolve B and collected by filtration, 0.524 g, mp 115–127°. Three recrystallizations from acetone–Skellysolve B gave **1-benzoyl-2-*n*-(2-hydroxy)propylpiperidine (30)** as colorless crystals: mp 128–131°; $[\alpha]_D$ 0° (chloroform); ν_{OH} 3460 w, 3400, 3300 w, $\nu_{C=O,C=C}$ 1625, 1605, 1590, 1580, 1525, 1495, ν_{Ph} 785, 745, 715 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 74 Hz (CH_3, doublet, J = 6.5 Hz, 3 H).

TABLE II

Fraction no.	Crude wt, g
7	1.12
8	3.98
9	7.02
10	4.99
11	3.10
12	2.18
13	1.57
14	0.60

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.64; H, 8.71; N, 5.42.

Fraction 9 was rechromatographed on a column of silica gel (500 g, 4.8 × 50 cm) packed as a slurry in benzene. Elution with 1% (v/v) methanol in benzene (500 ml) fractions gave pure (as detected by tlc on silica gel with 20% methanol–benzene development and Dragendorff spray) (+)-**1-benzoyl-2-*n*-propyl-3-piperidinol (26)** as a viscous oil (3.68 g) in fractions 21–27, $[\alpha]_D$ +51° (*c* 0.827, chloroform).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.15; H, 8.67; N, 5.82.

Crystals in fractions 11–14 of the Florisil column were washed with ether–Skellysolve and collected, 2.18 g, mp 110–118°. Three recrystallizations from acetone–Skellysolve B gave **1-benzoyl-2-*n*-propyl-4-piperidinol (27)** as colorless crystals: mp 122–123°; $[\alpha]_D$ −0.7° (chloroform); ν_{OH} 3360, $\nu_{C=O}$ 1600, $\nu_{C=C}$ 1575, 1525, 1500, ν_{Ph} 795, 735, 710 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 237 (4-H, six-line pattern, 1 H).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.09; H, 8.47; N, 5.59.

Oxidation of 30 with Jones reagent gave ketone **31**: nmr (in Hz, 37°, $CDCl_3$) 167 (CH_2CO, doublet, J = 7 Hz, 2 H), 131 (CH_3, singlet, 3 H).

Oxidation of 27 with Jones reagent gave ketone **29**: nmr (in Hz, 37°, $CDCl_3$) 287 (2-H, broad, 1 H), (6-H_{eq}, doublet, J = 13 Hz, 1 H), 198 (6-H_{ax}, multiple lines, 1 H), 175–130 (3- and 5-, multiple line, 4 H).

Oxygenation of 1-benzoyl-*cis*-2,6-dimethylpiperidine (32) (25.0 g, 0.115 mole) gave a total of 13.159 g (0.0565 mole, 49%) of crystalline (−)-**1-benzoyl-*cis*-2,6-dimethyl-3-piperidinol (33)**, mp 152–158°. Paper chromatography using the Bush B-3 system, tlc on silica gel with 20% (v/v) acetone in chloroform development, and vpc on 5% G.E. S. E. 52 on Gas Chrom Z and on 4% XE-60 on Haloport F columns all indicated only a single component in this product. Repeated recrystallizations from acetone–Skellysolve B gave an analytical sample of **33**: mp 147–157°; $[\alpha]_D$ −5 (*c* 0.913, chloroform); ν_{OH} 3360, $\nu_{C=O}$ 1630, $\nu_{C=C}$ 1610, 1595, 1515, 1495, V_{Ph} 710 cm^{-1} in Nujol; nmr (in Hz, 37°, $CDCl_3$) 274 (2- and 6-H, broad singlet, 2 H), 221 (3-H, four-line pattern having peak separation of 6 Hz, 1 H), 74 and 70 (CH_3, two doublets, J = 7 Hz, 6 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.86; H, 8.31; N, 6.33.

A second product, **34**, was obtained as 0.207 g (0.831 mmole, 0.7%) of colorless crystals, mp 263–265°, following two recrystallizations; $[\alpha]_D$ +2° (*c* 0.547, 95% ethanol); ν_{OH} 3400, 3240, $\nu_{C=O,C=C}$ 1615, 1585, 1530, 1490, ν_{Ph} 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.16; H, 7.55; N, 5.67.

Registry No.—**5**, 19980-00-8; **6**, 19980-01-9; **8**, 19980-02-0; **9**, 19980-03-1; **13**, 19980-04-2; **14**, 19980-05-3; **15**, 19980-06-4; **16**, 19980-07-5; **20**, 19980-08-6; **21**, 19980-09-7; **22**, 19980-10-0; **26**, 19980-83-1; **27**, 19990-84-2; **30**, 19990-85-3; **33**, 19990-86-4.

Acknowledgments.—We thank J. R. Heald, J. M. Noteboom, I. N. Pratt, M. J. Sutton, S. L. Towne, and H. M. Wiessner for technical assistance, and Dr. W. A. Struck and associates for physical and analytical data.

An Investigation of Stereochemistry and Migratory Aptitude in the Reductive Cyclization of β,β-Disubstituted o-Nitrostyrenes to 2,3-Disubstituted Indoles[1]

RICHARD J. SUNDBERG AND GEORGE S. KOTCHMAR, JR.

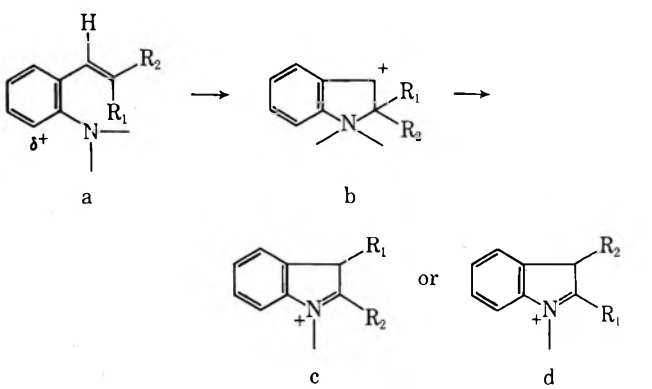
Department of Chemistry, University of Virginia, Charlottesville, Virginia

Received December 23, 1968

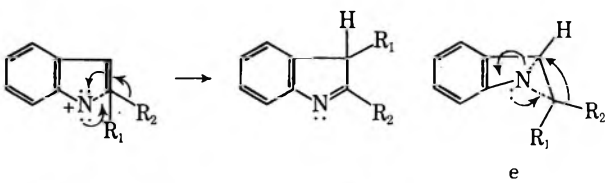
The syntheses of *cis*-α-methyl-2′-nitrostilbene (**2**) and *trans*-2-methyl-1-(*o*-nitrophenyl)-1-propene-3-d_2 (**3**) are reported. Deoxygenation of **2** in refluxing triethyl phosphite gives a 50% yield of 2-methyl-3-phenylindole and about 10% 1-ethyl-2-methyl-3-phenylindole. The product distribution in the deoxygenation of *trans*-α-methyl-2′-nitrostilbene (**1**) is almost identical under similar conditions. Deoxygenation of **3** gives a 20% yield of 2,3-dimethylindole consisting of equal parts of 2-methyl-3-methyl-d_2-indole and 2-methyl-d_2-3-methylindole. These results indicate that the configurational identity of the olefin substituents in the nitrostyrenes is lost before migration commences in these reductive cyclizations.

Deoxygenation of *o*-nitrostyrenes by trivalent phosphorus compounds leads to the formation of indoles.[2] β,β-Disubstituted *o*-nitrostyrenes cyclize with rearrangement of one of the β substituents to give 2,3-disubstituted indoles.[3] Three mechanisms[2,3] have been suggested for these reductive cyclizations and these are summarized, as they apply to the β,β-disubstituted *o*-nitrostyrene to 2,3-disubstituted indole transformation, in Scheme I. The electrophilic nitrogen atom which initiates cyclization could be a nitrene,[2] or the nitrogen atom of a nitroso group[3] or of a cyclic adduct of the nitro group and triethyl phosphite.[2b] No evidence which completely excludes any of these possibilities has been reported to date.[4]

SCHEME I

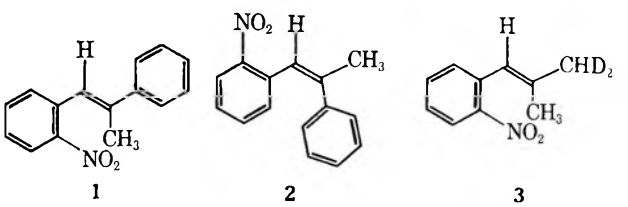


The β substituents labeled R_1 and R_2 are clearly in different stereochemical environments in the starting *o*-nitrostyrene, but, if structure b represents an intermediate or transition state in the reaction, R_1 and R_2 will become stereochemically equivalent and relative migratory aptitude would determine the extent to which each group migrates. On the other hand, if migration is concerted with cyclization as represented by transition state e, R_1 and R_2 could remain stereochemically unique throughout the course of the cyclizative rearrangement. Such a concerted migration seems feasible if the unshared pair on nitrogen were to promote migration as



cyclization proceeded. Stated in another way the question posed is essentially this: does R_2 (or R_1) begin to interact preferentially with the developing electron deficiency at C-3 before the symmetrical transition state b is reached?

In order to determine whether the original configuration of the *o*-nitrostyrene has any influence on the identity of the group which migrates during the cyclization, we have examined the deoxygenation of compounds **1**, **2**, and **3**.



Synthesis

The *trans*-*o*-nitrostilbene **1** was prepared by the literature procedure.[5] The *cis* isomer **2** was obtained from ethyl *trans*-*o*-nitro-α-phenylcinnamate (**5**) by the route outlined in Scheme II. Careful control of the reaction conditions permitted selective reduction of the carbethoxy group in **5** and of the alkyl bromide **8** without extensive reduction of the nitro group. The cinnamyl iodide (**9**) derived from **8** by halogen exchange was of no advantage in the reduction. The aldehyde **7** is a by-product of the reduction of **5**. Reduction of **5** at −10° gives mainly an azo coupling product.

The synthesis of **3** is outlined in Scheme III. The starting material is the cinnamaldehyde **10** which is expected to have the *trans* configuration by virtue of its preparation from *o*-nitrobenzaldehyde and propionaldehyde *via* aldol condensation and dehydration.[6]

Unlabeled **3**, prepared by Scheme III using sodium borohydride and lithium aluminum hydride in the reductions, was identical with a sample of **3** prepared from

(1) (a) Supported by NIH Grant GM-14344 and, in part, by National Science Foundation Grant GP-5292. (b) From the M. S. Thesis of G. S. Kotchmar, Jr., University of Virginia, Sept 1968.

(2) (a) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 4831 (1965); (b) R. J. Sundberg, *J. Org. Chem.*, **30**, 3604 (1965); (c) R. J. Sundberg, *ibid.*, **33**, 487 (1968).

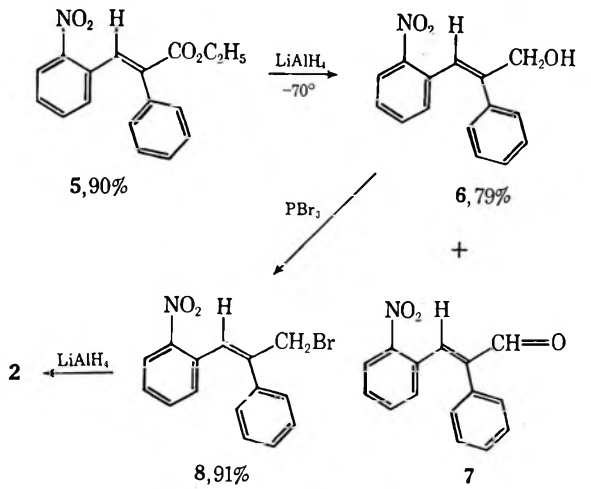
(3) R. J. Sundberg and T. Yamazaki, *ibid.*, **32**, 290 (1967).

(4) J. I. G. Cadogan, *Quart. Rev.* (London), **22**, 222 (1968).

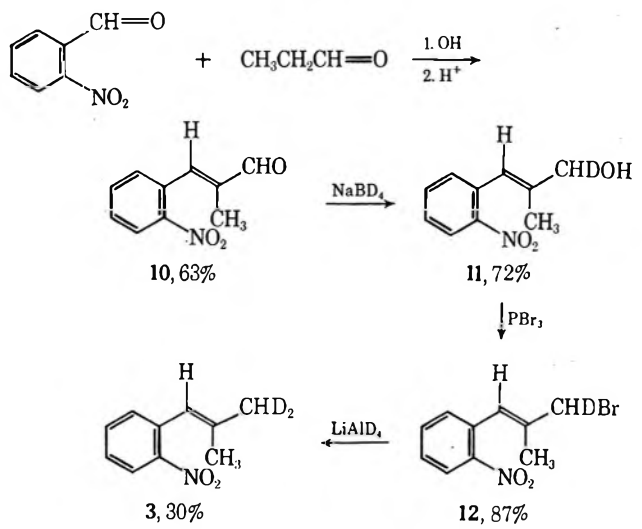
(5) A. V. Dombrovskii, Ya. G. Bal'on, and K. G. Tashchuk, *J. Gen. Chem. USSR*, **32**, 592 (1962).

(6) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 220, and references therein.

SCHEME II



SCHEME III



acetone and diethyl *o*-nitrobenzylphosphonate *via* a Wittig reaction.[3]

The nmr spectrum of **3** shows doublets in the nmr spectrum at δ 1.69 and 1.91 with integration ratios of 3:1, confirming the specific introduction of deuterium. Nonplanarity of the styrene system is indicated by the fact that the methyl group *cis* to the *o*-nitrophenyl group is more shielded than the *trans* group.[7] The nmr spectra of **1** and **2** show analogous behavior. The methyl group of **1** appears at δ 2.07 while the methyl signal in **2** is found at δ 2.24.

Deoxygenations

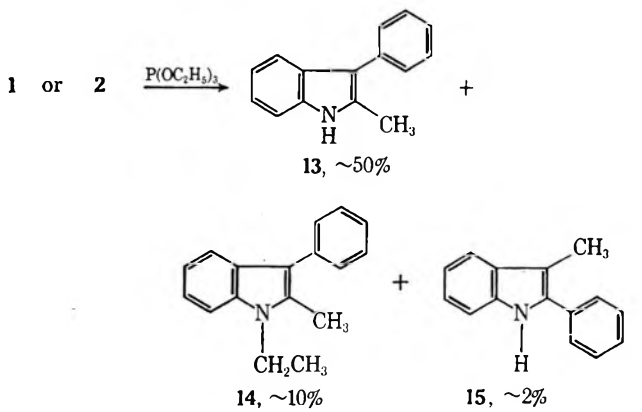
Deoxygenations of **1** and **2** were accomplished under comparable conditions in refluxing triethyl phosphite (6 hr). The major product from both nitrostyrenes was 2-methyl-3-phenylindole (**13**). Minor products included 1-ethyl-2-methyl-3-phenylindole (**14**), 3-methyl-2-phenylindole (**15**), and, probably, 1-ethyl-3-methyl-2-phenylindole (**16**). The yields as determined by isolation after column chromatography are summarized in Table I. The deoxygenation of **1** has been reported previously.[3] Compounds **13** and **14** were identified by spectral comparison with authentic samples.[3] The results of this work are in qualitative agreement with the previous work although the yields of **13** and **14** were found to be somewhat less than previously reported. The product of methyl migration, 3-methyl-2-phenylindole, has been identified as a component of the deoxygenation product by thin layer chromatography but it is present in too small an amount to permit isolation or detection by nmr. Nmr spectra of mixtures of **13** and **15** indicate that **15** would have been detectable by nmr if formed in a yield of 2% or more. Trace amounts of an oil having spectral properties in accord with expectation for **16** have been isolated. Phenyl migration appears to predominate by at least 25:1 over methyl migration in the deoxygenation of both **1** and **2** and the product mixture from both starting compounds is quite comparable.

TABLE I

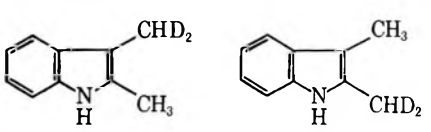
PRODUCT YIELDS FROM DEOXYGENATION OF *cis* AND *trans*-2-METHYL-2′-NITROSTILBENE

	Yield, %			
	13	**14**	**15**	**16**[a]
cis	54 (49)[b]	12 (12)[b]	<2	<1
trans	53 (53)[b]	9 (7)[b]	<2	<1

[a] Identification of this product is tentative. [b] Yield from duplicate experiment.



Deoxygenation of the deuterated β,β-dimethyl-*o*-nitrostyrene **3** gave a mixture of 2,3-dimethylindole (**17**, 22% yield) and 2,2-dimethyl-3-indolinone (**18**, 21% yield). These products have previously been characterized when isolated from undeuterated **3**.[3] The distribution of deuterium in **17** was investigated by nmr and by mass spectrometry. The nmr spectrum in benzene-d_6 shows the two methyl signals to be of equal intensity indicating that equal amounts of **17a** and **17b** have been formed by nonselective migration of the methyl and dideuteriomethyl groups. The parent peak in the mass spectrum of undeuterated **18** is shifted to 147 in the **17a**–**17b** mixture. The strong M − 15 peak[8] splits into peaks at 130 and 132 of nearly equal intensity in the dideuterated sample, again indicating that the deuterium is present in dideuteriomethyl groups equally distributed between C-2 and C-3.



(7) H. Rottendorf, S. Sternhell, and J. R. Wilmhurst, *Aust. J. Chem.*, **18**, 1759 (1965).

(8) J. H. Beynon, "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1960, p 399.

Control experiments have established that **1** and **2** are deoxygenated more rapidly than they are interconverted and that **3** is not converted into its geometrical isomer under the conditions of the deoxygenation reaction.

Discussion

The results from the deoxygenation of **3** show that the configuration of the nonequivalent methyl groups in the starting material does not have a measurable effect on the extent to which each of the groups migrates. This suggests that the methyl groups become stereochemically equivalent prior to migration. Similarly, the fact that **1** and **2** give predominantly the product of phenyl migration demonstrates that the configuration of the olefin is not an important factor in determining the identity of the migrating group. The fact that both **1** and **2** give a similar product mixture is consistent with the possibility that **1** and **2** give rise to a common intermediate. These results indicate that a structure such as b (Scheme I) represents an intermediate in the deoxygenation of β,β-disubstituted *o*-nitrostyrenes and rules out the possibility[3] that olefin configuration might play a part in determining which olefin substituent migrates. The relative phenyl–methyl migratory aptitude (>25:1) in **1** and **2** is consistent with mechanisms which involve migration to a carbonium ion site.

Experimental Section

General.—Commercial samples of triethyl phosphite were redistilled at atmospheric pressure under nitrogen. Silica gel H (Brinkmann Instruments) was used for thin layer chromatography and silicic acid powder (Mallinckrodt or Baker and Adamson) was used for column chromatography. Lithium aluminum hydride reductions were run under nitrogen.

Ethyl *trans*-*o*-Nitro-α-phenylcinnamate (5).—*trans*-*o*-Nitro-α-phenylcinnamic acid[9] was esterified with absolute ethanol and sulfuric acid in the normal manner giving **5** (90.6%), mp 57.4–58.4° (lit.[10] mp 59°).

Reduction of 5 with Lithium Aluminum Hydride. *trans*-*o*-Nitro-α-phenylcinnamaldehyde (7) and *trans*-*o*-Nitro-α-phenylcinnamyl Alcohol (6).—A solution of the ester **5** (10.0 g, 0.034 mol) in dry ether (80 ml) was cooled to about −70° with Dry Ice and ethanol. Lithium aluminum hydride (0.64 g, 0.017 mol) was refluxed in ether (150 ml) for 30 min and the resulting suspension was added to the ester solution through a dropping funnel over a period of 1 hr. The reaction mixture was stirred for 15 min and excess hydride was destroyed by successive addition of ethanol (20 ml), moist ether (40 ml), and water (40 ml). The temperature of the reaction mixture was allowed to rise to −5° and then 10% sulfuric acid (300 ml) was added. The reaction mixture was extracted with ether and the crude product was chromatographed on silicic acid (200 g). Benzene eluted unreacted **5** (3.3 g, 0.011 mol) and *trans*-*o*-nitro-α-phenylcinnamaldehyde (**7**, 0.6 g, 0.0024 mol, 10.5%): mp 92–94° after crystallization from ethanol; $\nu_{C=O}$ 1680 cm^{-1}; ν_{NO_2} 1515, 1340 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 222 mμ (log ε 4.27), 268 (4.07); nmr peaks ($CDCl_3$) at δ 6.8–8.3 (9 H, multiplet), 7.8 (1 H, s), 9.88 (1 H, s).

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.30; H, 4.38; N, 5.54. Found: C, 71.25; H, 4.50; N, 5.38.

Later benzene fractions contained *trans*-*o*-nitro-α-phenylcinnamyl alcohol (**6**), a yellow oil (4.6 g, 0.018 mol, 80%) which was purified by short-path distillation: bp 198–200° (0.3 mm); ν_{OH} 3375, 3555 cm^{-1}; ν_{NO_2} 1520, 1345 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (log ε 4.03), 255 (3.97); nmr peaks ($CDCl_3$) at 2.27 (1 H, s), 4.54 (2 H, d), 7.02 (1 H, s), 6.8–8.0 (9 H, multiplet).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.60; H, 5.14; N, 5.50. Found: C, 70.88; H, 5.31; N, 5.77.

A similar reduction run at −10° gave a 40% yield of 2,2′-azo-α-phenylcinnamyl alcohol: mp 172–174°; ν_{OH} 3420 cm^{-1}; nmr peaks (DMSO-d_6) at δ 4.38 (4 H, d), 5.27 (2 H, t), 7.0 (2 H, s) and 7.1–7.8 (18 H, multiplet).

Anal. Calcd for $C_{30}H_{26}N_2O_2$: C, 80.70; H, 5.88; N, 6.32. Found: C, 80.53; H, 6.09; N, 6.12.

***trans*-*o*-Nitro-α-phenylcinnamyl Bromide (8).**—A solution of the alcohol **6** (3.0 g, 0.012 mol) in ether (10 ml) was cooled to −10° and a solution of phosphorus tribromide (1.2 g, 0.0045 mol) in ether (20 ml) was slowly added. The reaction mixture was allowed to warm to room temperature and stirred for 5 hr.

The reaction mixture was poured onto ice and extracted with ether (100 ml). The ether layer was washed with dilute sodium carbonate, dried over sodium sulfate, and concentrated giving crystalline **8** (3.4 g, 0.011 mol, 92%): mp 87–88° after recrystallization from 8:2 hexane–benzene; ν_{NO_2} 1510, 1355 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 239 mμ (log ε 4.09), 263 (4.03); nmr peaks ($CDCl_3$) at δ 4.43 (2 H, d) and 6.75–8.1 (10 H, multiplet).

Anal. Calcd for $C_{15}H_{12}NO_2Br$: C, 56.50; H, 3.80; N, 4.40. Found: C, 56.36; H, 3.68; N, 4.27.

***trans*-*o*-Nitro-α-phenylcinnamyl Iodide (9).**—The bromide **8** (1.5 g, 0.0047 mol) was stirred with sodium iodide (0.71 g, 0.0047 mol) in acetone (25 ml) at 50° for 45 min. After filtration, the reaction mixture was diluted with benzene and washed with sodium thiosulfate. Concentration of the dried benzene solution gave **9** which was recrystallized from 8:2 hexane–benzene (1.1 g, 0.003 mol, 64%): mp 104–105°; ν_{NO_2} 1520, 1340 cm^{-1}; nmr peaks ($CDCl_3$) at 4.36 (2 H, s) and 6.7–8.0 (10 H, multiplet).

Anal. Calcd for $C_{15}H_{12}NO_2I$: C, 49.4; H, 3.32; N, 3.84. Found: C, 49.58; H, 3.10; N, 3.72.

***cis*-α-Methyl-2′-nitrostilbene (2).**—A solution of the bromide **8** (5.0 g, 0.016 mol) in ether (100 ml) was added dropwise over 20 min to a suspension of lithium aluminum hydride (0.372 g, 0.0098 mol) in dry ether (90 ml). After addition was complete, the solution was refluxed for 2.5 hr. After cooling, excess lithium aluminum hydride was destroyed by addition of moist ether and then water. The reaction mixture was hydrolyzed with 10% sulfuric acid and extracted with ether. The crude product was purified by chromatography on silicic acid (150 g). Hexane–benzene (8:2) eluted **2** as a yellow oil (1.5 g, 0.0063 mol, 52%): ν_{NO_2} 1520, 1340 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (log ε 4.03), 256 (4.00); nmr peaks ($CDCl_3$) at δ 2.24 (3 H, d), 6.7 (1 H, d), and 6.8–8.0 (9 H, multiplet).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.49; N, 5.86. Found: C, 75.18; H, 5.30; N, 5.69.

Unreacted bromide (1.3 g, 0.0041 mol) was eluted with 6:4 hexane–benzene.

***trans*-α-Methyl-*o*-nitrocinnamaldehyde (10).**—*o*-Nitrobenzaldehyde (7.5 g, 0.050 mol) and propionaldehyde (8.7 g, 0.15 mol) were dissolved in ether (40 ml). There was added 60 ml of a solution prepared by diluting 8 ml of 25% aqueous sodium hydroxide with 200 ml of ethanol. The reaction mixture was stirred for 18 hr and then extracted with water. The ether layer was dried over magnesium sulfate and evaporated, leaving a yellow oil with spectral properties in accord with those expected for the intermediate aldol condensation product. The oil was dissolved in benzene (300 ml), *p*-toluenesulfonic acid (2.1 g) was added, and the solution was refluxed for 75 min. The benzene solution was washed with water and dilute sodium bicarbonate and then concentrated leaving a black oil. Vacuum distillation gave *o*-nitrobenzaldehyde (1.9 g, 0.013 mol) and **10** (4.5 g, 0.023 mol, 64%): bp 130–131° (0.25 mm); $\nu_{C=O}$ 1685 cm^{-1}; ν_{NO_2} 1520, 1340 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.9 (3 H, d), 7.5–8.5 (5 H, multiplet) and 9.8 (1 H, s).

The analytical sample was prepared by chromatography using a silicic acid column and benzene as the eluent.

Anal. Calcd for $C_{10}H_9NO_3$: C, 62.90; H, 4.74; N, 7.33. Found: C, 62.87; H, 4.75; N, 7.06.

***trans*-α-Methyl-*o*-nitrocinnamyl Alcohol-d_1 (11).**—A solution of **10** (5 g, 0.026 mol) in methanol (25 ml) which had been adjusted to pH 8 was added dropwise to sodium borodeuteride (0.30 g, 0.0079 mol) in methanol (30 ml) which had been adjusted to pH 8 with aqueous sodium hydroxide. The solution was stirred for 1.5 hr and diluted with water. The reaction mixture was extracted with ether and the extract was dried over magnesium sulfate, leaving **11** as a yellow oil (3.7 g, 0.019 mol, 72%): ν_{OH} 3325; ν_{NO_2} 1520, 1350 cm^{-1}. The compound showed tlc behavior identical with an undeuterated sample.

Undeuterated **11** was prepared in 77% yield using sodium borohydride: nmr peaks ($CDCl_3$) at δ 1.71 (3 H, d), 2.92 (1 H, broad singlet), 4.25 (2 H, broad singlet), 6.8 (1 H, s, broad), and

(9) D. F. DeTar and Y. W. Chu, *J. Amer. Chem. Soc.*, **76**, 1686 (1954).

(10) F. K. Beilstein, "Handbuch der organischen Chemie," Vol. 9, 1918, p 694.

7.25–8.11 (4 H, multiplet). The analytical sample was purified by chromatography on silicic acid using 8:2 benzene–ether as the eluent.

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.20; H, 5.74; N, 7.24. Found: C, 62.42; H, 5.87; N, 6.88.

trans-α-**Methyl-o-nitrocinnamyl Bromide-d_1 (12).**—Phosphorus tribromide (1.98 g, 0.0073 mol) in dry ether (25 ml) was added dropwise to deuterated **11** (3.7 g, 0.019 mol) in dry ether (42 ml) at −10°. After addition of phosphorus tribromide was complete, the solution was stirred at room temperature for 7 hr. The reaction mixture was poured onto ice and extracted with ether. The ether was washed with aqueous sodium carbonate, dried over magnesium sulfate, and concentrated. The residual oil was distilled, giving a yellow oil (4.3 g, 0.017 mol, 87%): bp 111–113° (0.1 mm); ν_{NO_2} 1520, 1340 cm^{-1}.

An undeuterated sample was prepared by an identical procedure from unlabeled **11**: nmr peaks ($CDCl_3$) at δ 1.87 (3 H, d), 4.17 (2 H, d), 6.96 (1 H, broad singlet) and 7.30–8.20 (4 H, multiplet).

Anal. Calcd for $C_{10}H_{10}NO_2Br$: C, 46.90; H, 4.21; N, 5.46. Found: C, 47.00; H, 3.97; N, 5.50.

trans-**2-Methyl-1-(*o*-nitrophenyl)-1-propene-3-d_2.**—A solution of deuterated **11** (5.0 g, 0.019 mol) in dry ether (70 ml) was added dropwise to lithium aluminum deuteride (0.412 g, 0.0098 mol) in dry ether (75 ml). After addition was complete, the reaction mixture was refluxed for 2.5 hr. Excess lithium aluminum deuteride was destroyed with moist ether and water and the reaction mixture was hydrolyzed with 10% sulfuric acid. The ether layer was washed with water, dried, and evaporated. Chromatography of the residual oil on silicic acid gave **3** (1.07 g, 0.0060 mol, 30%): ν_{NO_2} 1520, 1340 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.69 (3 H, d), 1.91 (1 H, d), 6.48 (1 H, broad singlet), and 7.1–8.0 (4 H, multiplet). Except for the diminished intensity of the signal at δ 1.91, the nmr spectrum is identical with an unlabeled sample of **3** from unlabeled **12** and with a sample previously prepared by an independent procedure.[3]

Standard Deoxygenation Procedure.—The nitrostyrene was refluxed with a 6 *M* ratio of triethyl phosphite under a nitrogen atmosphere for 6 hr. The solution was cooled and triethyl phosphite [bp ~25° (0.1 mm)] and triethyl phosphite [bp 43–46° (0.2 mm)] were removed by vacuum distillation. The residue was dissolved in ether, washed with water, dried, and concentrated. The residue was chromatographed on silicic acid (60–70 g, packed as a slurry in hexane). The solvent sequence was hexane, 9:1 hexane–benzene, 4:1 hexane–benzene, 1:1 hexane–benzene, and 9:1 benzene–ether. The course of the chromatography was followed by tlc.

Deoxygenation of *trans*-α-Methyl-2′-nitrostilbene (1).—Deoxygenation of **1** (3.1 g, 0.013 mol) gave an oil (0.016 g) eluted by hexane and tentatively identified as **16** on the basis of an nmr spectrum: nmr peaks at δ 1.2 (t), 2.3 (s), 4.2 (q) 7.0–7.8 (multiplet). Hexane–benzene (9:1) eluted **14** as an oil (0.28 g, 0.0012 mol, 9%) which was identified by spectral comparison with an authentic sample.[3] Hexane–benzene (1:1) eluted **13** (1.43 g, 0.0069 mol, 53%) containing **15** as a contaminant as shown by tlc comparison with authentic **15**. The methyl signal of **15** at δ 2.34 was not discernible in the nmr spectrum (<2% yield). The infrared and nmr spectrum of the product were identical with an authentic sample of **13**.[11]

Deoxygenation of *cis*-α-Methyl-2′-nitrostilbene (2).—Deoxygenation of **2** (2.5 g, 0.010 mol) gave **14** (0.39 g, 0.0012 mol, 12%), **13** (1.13 g, 0.0055 mol, 54%), and a 1:1 mixture of **14** and **15** (0.035 g, 0.8% yield of each) as identified by tlc and nmr spectral data.

Deoxygenation of β,β-Dimethyl-*o*-nitrostyrene-d_2 (3).—Deoxygenation of **3** (1.50 g, 0.0084 mol) gave **17** (0.28 g, 0.0019 mol, 22%) which was eluted with 1:1 hexane–benzene and identified by tlc and nmr comparison with unlabeled **17**. The integrated intensity of the peaks at δ 1.80 and 2.10 in benzene-d_6 were identical. Benzene–ether (9:1) eluted 2,2-dimethyl-3-indolinone (0.30 g, 0.0018 mol, 22%) which was identified by tlc and infrared data. A deoxygenation of unlabeled **3** gave similar product yields.

Control Experiment.—Partial deoxygenation of *cis*-α-methyl-2′-nitrostilbene (1 hr) permitted recovery of 10% of the nitrostilbene shown by nmr to be an 83:17 mixture of **2** and **1**, indicating that thermal isomerization of **2** to **1** is slow relative to deoxygenation.

Partial deoxygenation of **3** (1 hr) permitted recovery of 5.5% of unreacted **3**. The nmr spectrum of **3** showed a 1:3 integration ratio for the peaks at δ 1.9 and 1.7 indicating no interchange of the methyl and methyl-d_2 groups.

Registry No.—**2**, 20072-75-7; **3**, 20072-76-8; **6**, 20072-77-9; **7**, 20072-78-0; **8**, 20072-79-1; **9**, 20072-83-7; **10**, 20072-80-4; **11**, 20072-81-5; **12**, 20072-82-6; **11** (undeuterated), 20073-27-2; **12** (undeuterated, 20073-28-3; 2,2′-azo-α-phenylcinnamyl alcohol, 20072-84-8.

(11) E. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 612 (1953).

The Enol Acetylation of Alkylated Δ⁴-3-Oxo Steroids. A Novel Enone–Phenol Transformation

A. J. LISTON AND P. TOFT

Research Laboratories, Food and Drug Directorate, Department of National Health and Welfare, Ottawa, Canada

Received December 3, 1968

The perchloric acid catalyzed acetic anhydride acylation of a number of mono- and dialkylated steroids at the C-2 and C-6 positions has been investigated. In those cases where $\Delta^{2,4}$-dienol acetate formation is favored a novel hydride abstraction reaction is described which leads to intermediates which undergo dienone–phenol rearrangement. In contrast, the isopropenyl acetate enol acetylation of these compounds invariably led to the exclusive formation of $\Delta^{3,5}$-dienol acetate except in the one instance where the presence of a 6β substituent resulted in a 1:1 mixture of $\Delta^{2,4}$- and $\Delta^{3,5}$-dienol acetates.

As part of a program to examine the influence of remote substituents on the enolization properties of Δ⁴-3-oxo steroids, we have been studying the perchloric acid catalyzed acetic anhydride enol acetylation of steroids. The enol acetylating conditions chosen are known to reflect the enolization properties of saturated keto steroids.[1] However, in a previous study[2] with conjugated ketones it was demonstrated that under these conditions the enol acetylation reaction leads to mixtures of O- and C-acylated products. The major products from the reaction of 17β-hydroxyandrost-4-en-3-one (**1a**) were 3,17β-diacetoxy-2-acetylandrosta-2,4-diene and 3,17β-diacetoxy-6-acetylandrosta-3,5-diene. The C-acylation reaction was shown to proceed *via* the intermediate $\Delta^{3,5}$- and $\Delta^{2,4}$-dienol diacetates. The subsequent acetylium ion[3] attack on the isomeric

(1) A. J. Liston, *J. Org. Chem.*, **31**, 2105 (1966).

(2) A. J. Liston and P. Toft, *ibid.*, **33**, 3109 (1968).

(3) The identity of the acetylating species in perchloric acid catalyzed enol acetylations has not been unequivocally established. However, there is increasing evidence that this ion must play a significant role [*cf.* D. P. N. Satchell, *Quart. Rev.* (London), **17**, 196 (1963)].

dienol diacetates effectively prevented any study of the equilibrium between the isomeric enolic forms.

To eliminate the foregoing difficulties alkylated Δ⁴-3-oxo steroids were studied. The incorporation of alkyl groups at the C-2 and C-6 positions of the steroid nucleus would be expected to render the dienol acetates impervious to acetylium ion attack since it has been shown by Gorodetsky[4] that tetrasubstituted double bonds are not susceptible to attack by this ion.

For this study a series of alkylated steroids was prepared. They are 17β-acetoxy-2α-methylandrost-4-en-3-one (**1c**), 17β-acetoxy-2α-ethylandrost-4-en-3-one (**1d**), 2α,6β-dimethyl-17β-hydroxyandrost-4-en-3-one (**1h**), and 6α-methylandrost-4-en-3-one (**1e**). The first compound, **1c**, was prepared in 65% yield by methylation of the ethoxyoxalate derivative of testosterone (**1a**) with methyl iodide.[5] Elimination of the oxalyl moiety was carried out with sodium ethoxide in ethanol and the product, 2α-methyltestosterone (**1f**), was acetylated with pyridine–acetic anhydride mixture to yield compound **1c**. The 2α-ethyl analog **1g** was prepared by the same method using ethyl iodide as alkylating agent.[6] The product **1g** was treated as before to yield the corresponding acetate **1d**.

The 2α,6β-dimethyl steroid **1h** was prepared from 17β-hydroxy-2α-methylandrost-4-en-3-one (**1f**). Ketalization of **1f** gave only one product, the 3,3-ethylenedioxy derivative **2**, in which the location of the double bond was established by nmr spectroscopy.[7-10] The ketal **2** was treated with *m*-chloroperbenzoic acid to form a mixture of epoxides which were identified by their rotations. It has been established[11] that the epoxidation of Δ⁵-3,3-ethylenedioxy compounds gives predominantly the α-epoxide. Glpc analysis of the crude reaction product demonstrated two products, the less polar β-epoxide **4** (30%) and the more polar α-epoxide **3** (70%), the more levorotatory compound **3** being assigned the α configuration. These assignments were confirmed by nmr spectroscopy. The 6β-proton signal of the α-epoxide **3** was located at δ 2.78 in the nmr spectrum; the doublet had the characteristic coupling constant, J = 4 Hz, whereas the doublet due to the 6α proton of the β-epoxide **2** was situated at δ 3.03 with the characteristic coupling constant, J = 2 Hz.[12] The α-epoxide **3** was treated with methylmagnesium iodide to yield 3,3-ethylenedioxy-2α,6β-dimethylandrosta-5α,17β-diol (**5a**). The stereochemistry of the product was assigned by analogy with previous work on similar compounds.[13] The ketal group was removed by hydrolysis with acetic acid to yield the ketodiol **5b** which was dehydrated with dilute aqueous methanolic sodium hydroxide.[13a]

In view of the strong C-6–C-10 diaxial methyl interaction it had been expected that prolonged base treatment such as employed in the dehydration reaction would effect concomitant epimerization of the C-6 methyl substituent.[14] The nmr spectrum of the product suggested that the stereochemistry at C-6 was not altered. The location of the C-19 methyl signal at δ 1.28 was in agreement with the calculated value for a 6β-methyl substituent.[15a] Further, the lack of allylic coupling between the C-4 vinylic proton and the α proton at C-6 corroborated the assignment.[15b] Under acidic conditions the compound underwent facile isomerization to yield the 2α,6α-dimethyl product **1j**. These equilibration results are in agreement with those of Malhotra and Ringold[16] in which enolization toward the Δ³,⁵ position is disfavored under basic conditions.

The model compound **1e** was prepared from 3β,17α-dihydroxy-6-methylpregn-5-en-20-one (**6**) by treatment with sodium borohydride to form an epimeric mixture of C-20 alcohols which was cleaved with sodium periodate (Scheme I).[17] The product, 3β-hydroxy-6-methylandrost-5-en-17-one (**7**), was converted into 6-methylandrost-5-en-3β-ol (**8**) by Wolff–Kishner reduction. Oppenauer oxidation of **8** with aluminum *t*-butoxide afforded 6α-methylandrost-4-en-3-one (**1e**).[18,19]

The enol acetylation of 17β-acetoxy-2α-methylandrost-4-en-3-one (**1c**) using isopropenyl acetate–sulfuric acid catalyst gave an excellent yield of 3,17β-diacetoxy-2α-methylandrosta-3,5-diene (**10a**) (Scheme II). The compound was identified by comparison of the uv spectrum with that of 3,17β-diacetoxyandrosta-3,5-diene.[20] The identity of compound **10a** was confirmed by nmr spectroscopy which demonstrated signals due to the two vinylic protons at C-4 and C-6. Compound **10a** was treated under equilibrating conditions using a solution of acetic anhydride in benzene–carbon tetrachloride containing a trace of perchloric acid catalyst.[2] After 6 hr glpc analysis demonstrated the formation of two major components in a ratio of 23% (**14a**) and 77% (**13a**). Treatment of 2α-methyltestosterone (**1f**) with acetic anhydride–perchloric acid reagent gave essentially the same results. Glpc analysis indicated that the starting material **1f** was rapidly converted (10 min) into 3,17β-diacetoxy-2α-methylandrosta-3,5-diene (**10a**) and then followed the same reaction pathway leading to the two major products previously detected.

(4) M. Gorodetsky, E. Levy, R. D. Youssefyeh, and Y. Mazur, *Tetrahedron*, **22**, 2039 (1966).

(5) (a) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Amer. Chem. Soc.*, **81**, 427 (1959); (b) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(6) A similar low yield in preparing a 2α-ethyl derivative was reported by J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Amer. Chem. Soc.*, **77**, 6401 (1955).

(7) The fact that no Δ⁴-3-ketal was obtained from the 2α-methyl compound **1f** suggests that the Δ²,⁴-dienol ether[8] is not an intermediate of the ketalization reaction, and rather supports the mechanism proposed by Djerassi[9] and Christiansen.[10]

(8) J. J. Brown, R. H. Lenhard, and S. Bernstein, *J. Amer. Chem. Soc.*, **86**, 2183 (1964).

(9) C. Djerassi and M. Gorman, *ibid.*, **75**, 3704 (1953).

(10) J. W. Dean and R. G. Christiansen, *J. Org. Chem.*, **28**, 2110 (1963).

(11) A. Bowers, L. C. Ibanez, and J. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

(12) A. D. Cross, *J. Amer. Chem. Soc.*, **84**, 3206 (1962).

(13) (a) S. Bernstein and R. Littell, *ibid.*, **82**, 1235 (1960); (b) G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

(14) *Cf.* J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Amer. Chem. Soc.*, **80**, 4717 (1958).

(15) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1966: (a) p 14; (b) p 109.

(16) S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 1997 (1964).

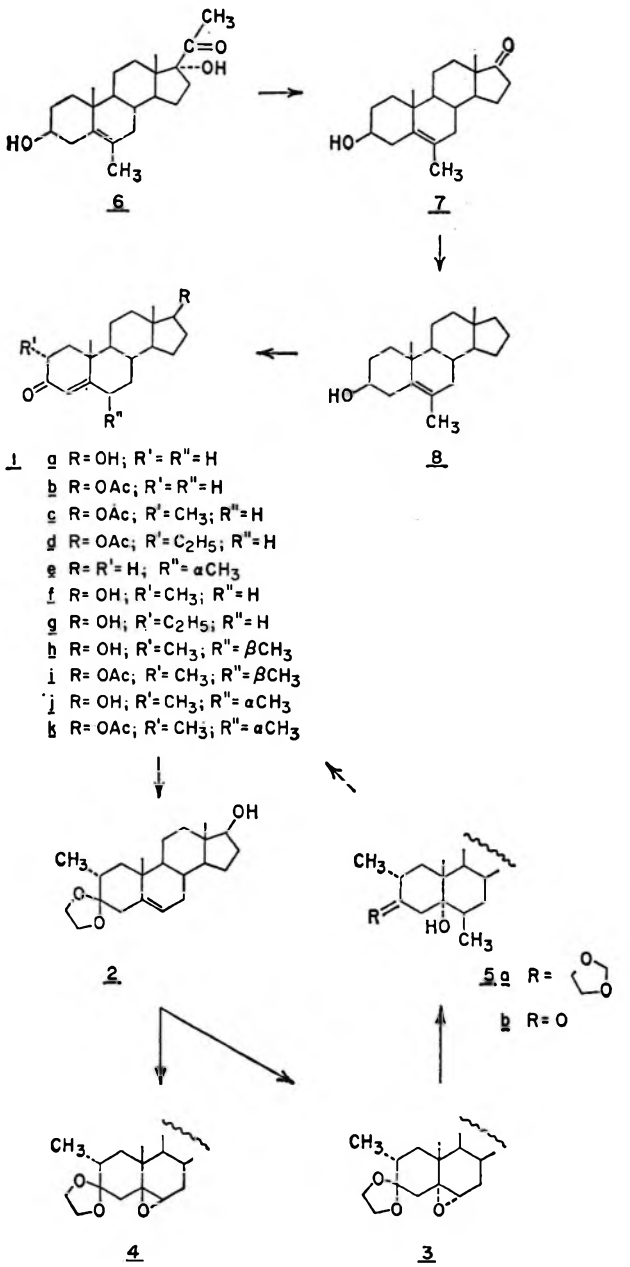
(17) A. J. Liston and M. Howarth, *J. Org. Chem.*, **32**, 1034 (1967).

(18) The oxidation of 3-hydroxy Δ⁵-steroids by chromic acid or chromium trioxide is known to give erratic results;[19] however, the milder pyridine–chromium trioxide reagent was used in an attempt to prepare the Δ⁴-3-ketone **1e**. By allowing compound **8** to stand at room temperature in the presence of an excess of oxidizing agent for 40 hr, a 20% yield of 6β-hydroxy-6α-methylandrost-4-en-3-one (**16**) was isolated. The stereochemistry at C-6 was assigned on the basis of the nmr spectrum. The location of the C-19 angular methyl signal at 85 Hz was in agreement with the calculated value whereas the epimeric compound would be expected to have the C-19 signal at 75 Hz.[15a]

(19) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 202.

(20) (a) R. H. Cox and E. Y. Spencer, *Can. J. Chem.*, **29**, 398 (1951); (b) U. Westphal, *Naturwissenschaften*, **24**, 696 (1936); (c) U. Westphal, *Ber.*, **70**, 2128 (1937).

SCHEME I



The major constituent **13a** of the reaction mixture was isolated by column chromatography. The mass spectrum of the product demonstrated a molecular ion peak at *m/e* 470 and the uv spectrum with a maximum at 288 mμ suggested a complex polyacetylation product. The salient features of the nmr spectrum were a vinylic one-proton singlet, a one-proton multiplet due to a hydrogen geminal with an acetate function,[21] five methyl signals between 98 and 130 Hz, and two angular methyl signals. The lack of the 2α-methyl doublet at δ 0.98, observed in spectrum of compound **10a**, indicated a $\Delta^{2,4}$-dienic structure. The 6-(1′-acetoxyethylidene)-3,17β-diacetoxy-2α-methylandrosta-2,4-diene (**13a**) structure was assigned to the compound. The assignment was verified by mild saponification with aqueous sodium acetate[4] which yielded a mixture of epimeric C-6 methyl ketones of which 6β-acetyl-17β-acetoxy-2α-methylandrost-4-en-3-one (**15a**) was the major constituent. The compounds were separated by column chromatography and the major constituent **15a** had a uv maximum (246 mμ) which shifted (to 428 mμ) in ethanolic potassium hydroxide. The bathochromic shift in base and the location of these maxima is characteristic for the 6-acetyl-Δ^4-3-ketone chromophore.[2,4] The nmr spectrum of the compound was consistent with structure **15a**, the signals due to the methyl ketone appearing at δ 2.12 and the 6α hydrogen as a doublet centered at δ 3.24 with J = 4.5 Hz. These features of the spectrum were identical with those of 6β-acetyl-17β-acetoxyandrost-4-en-3-one previously prepared.[2,4] The minor constituent of the mixture, the 6α-acetyl derivative was isolated and demonstrated a uv spectrum (240 mμ) which underwent a bathochromic shift under alkaline conditions (to 428 mμ). Insufficient material was available to characterize the product completely.

The second constituent **14a** of the reaction product was isolated by column chromatography and its nmr spectrum indicated one angular methyl signal (C-18), four methyl signals at lower field (δ 2.25–2.05), and a single olefinic proton signal. The molecular weight determined by mass spectrometry was 384 which suggested the molecular formula $C_{24}H_{37}O_4$. The ir and uv spectra were consistent with a phenolic steroid in which migration of the angular methyl group *via* dienone–phenol rearrangement had occurred. If the transformation follows the conventional dienone–phenol type of rearrangement the product could have the aromatic methyl substituents at positions 1 and 2, 2 and 3, or 2 and 4.[22,23] It was not possible to predict the mechanistic pathway since previous examples of this rearrangement were limited to steroids having three or more double bonds in the ring A and B portion of the steroid[24] and hence did not involve an oxidative step.

Proof that the compound was in fact 1,17β-diacetoxy-2,4-dimethylestra-1,3,5(10)-triene (**14a**) was obtained by independent synthesis. The compound was prepared from **1f** by selenium dioxide dehydrogenation[25] to yield the dienone **11a**. Dienone–phenol rearrangement was carried out in acetic anhydride–*p*-toluenesulfonic acid.[24] The product was identical with the compound isolated in the enol acetylation of **1c**. The identity was further confirmed by saponification of the acetate functions and by comparing the 2,4-dimethylestra-1,3,5(10)-triene-1,17β-diol (**14c**) with authentic material.

The enol acetylation of 17β-acetoxy-2α-ethylandrost-4-en-3-one (**1d**) was studied using identical conditions. The $\Delta^{3,5}$-dienol diacetate **10b** was prepared by the isopropenyl acetate method and identified by comparison of its spectral properties with those of the corresponding 2α-methyl derivative **10a**. Treatment of the dienol diacetate **10b** with perchloric acid–acetic anhydride mixture gave similar results. Two major products were detected by glpc analysis and separated by column chromatography. The major constituent (90%) was 6-(1′-acetoxyethylidene)-3,17β-diacetoxy-2-ethylandrosta-2,4-diene (**13b**). The compound was identified by mass spectrometry and by comparison of its

(21) S. G. Levine, N. H. Eudy, and C. F. Leffler, *J. Org. Chem.*, **31**, 3995 (1966).

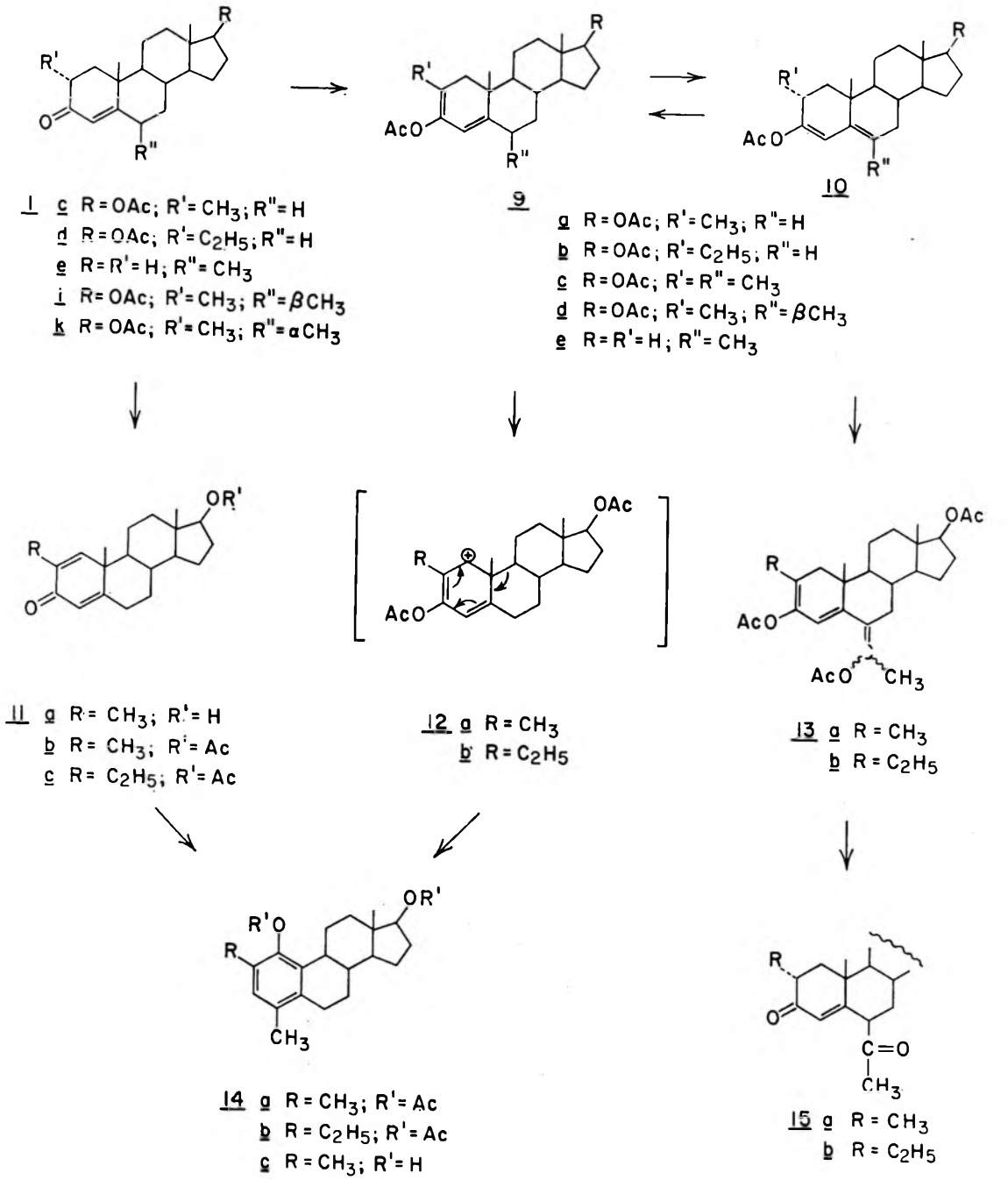
(22) R. B. Woodward and T. Singh, *J. Amer. Chem. Soc.*, **72**, 429 (1950).

(23) W. H. Hopff and A. S. Dreiding, *Angew. Chem. Intern. Ed. Eng.*, **4**, 690 (1965).

(24) C. Djerassi, "Steroid Reactions," Holden-Day Inc., San Francisco, Calif., 1963, p 373.

(25) J. Iriarte and H. J. Ringold, *Tetrahedron*, **3**, 28 (1958).

SCHEME II



spectral properties with those of the 2α analog **13a**. The structure **13b** was confirmed by saponification with aqueous sodium acetate to yield a mixture of C-6 epimers of 17β-acetoxy-6-acetyl-2α-ethylandrost-4-en-3-one (**15b**). The minor constituent of the reaction (10%) was 1,17β-diacetoxy-2-ethyl-4-methylestra-1,3,5(10)-triene (**14b**).[26] The compound demonstrated the necessary spectral properties for the assigned structure. The proof of structure was obtained by independent synthesis of the compound *via* the intermediate 17β-acetoxy-2-ethylandrost-1,4-dien-3-one (**11c**) which was subjected to the dienone–phenol rearrangement.

(26) The content of transformation product **14b** was difficult to assess accurately by glpc analysis because the peak was coincident with that of the $\Delta^{3,5}$-dienol diacetate **10b**. The estimate was made at that point when there was no further variation in the peak height relative to that of the major product **18b**.

Treatment of 2α,6β-dimethyl-17β-hydroxyandrost-4-en-3-one (**1h**) with isopropenyl acetate gave a mixture of enol acetates which varied with the catalyst used in the reaction. Using sulfuric acid catalyst the ratio of $\Delta^{3,5}$- (**10c**) to $\Delta^{2,4}$-dienol acetate (**9d**) was 85:15. When *p*-toluenesulfonic acid was used as catalyst the ratio of products formed was 50:50. The compounds were separated by column chromatography using 10% silver nitrate on Florisil. The $\Delta^{3,5}$-dienol acetate **10c** was identified by comparison of its spectral properties with those of the previously prepared 2α-methyl analog (**10a**). The $\Delta^{2,4}$-dienol diacetate **9d** structure was assigned on the basis of its uv spectrum (269 mμ which is characteristic for a homoannular diene. Proof that the compound was isomeric with **10c** was obtained by treating the dienol diacetate **9d** with the perchloric acid–acetic anhydride mixture. The com-

pound was completely isomerized to the $\Delta^{3,5}$-dienol diacetate **10c** at room temperature within 30 min. The *p*-toluenesulfonic acid catalyzed isopropenyl acetate enol acetylation of the epimeric 2α,6α-dimethyl steroid **1k** yielded a single $\Delta^{3,5}$-dienol diacetate **10c**.

Isopropenyl acetate enol acetylation of 6α-methylandrost-4-en-3-one (**1e**) gave a single enol acetate, 3-acetoxy-6-methylandrosta-3,5-diene (**10e**), which was stable to the perchloric acid–acetic anhydride equilibrating conditions. The structural assignment was made on the basis of the nmr and uv spectra.

Traces of phenolic products (3%) have previously been detected in the perchloric acid catalyzed enol acetylation of Δ^1-3-oxo-5α steroids.[27] The formation of such compounds was ascribed to dienone–phenol rearrangement of an intermediate 1,4-dien-3-one which arose from perchloric acid oxidation of the starting Δ^1-3-ketone. This hypothesis was tested by treating compound **1f** under the perchloric acid conditions except that acetic acid was substituted for the anhydride. Careful glpc analysis of the mixture at 24 hr revealed no trace of secondary products. Similarly glpc analysis of the crude acetylation product of **1c** was devoid of a signal which corresponded to the proposed intermediate **11a**.[28] These results signify that the transformation of the 2α-methyl steroid **10a** does not occur by the intermediacy of an oxidation product formed directly by the action of perchloric acid to give a dienone which subsequently undergoes conventional dienone–phenol rearrangement.

Discussion

Examination of the perchloric acid catalyzed enol acetylation results indicates that only two model compounds formed phenolic products; the 2α-methyl steroid **1c** formed 22.8% **14a** and the 2α-ethyl compound **1d** formed 10% **14b**. These results suggest that in compounds such as **1b**, **1e**, and **1i** where the $\Delta^{3,5}$-dienol acetate structure **10** would be expected to be more stable there is no formation of phenolic products. However, in those compounds where the 2-alkyl substituent stabilizes the $\Delta^{2,4}$-dienol acetate structure **9** phenolic products are formed. Since the 2-methyl substituent has a greater hyperconjugative effect than the 2-ethyl substituent it is consistent that more phenol is formed in the methyl series if the transformation is dependent on $\Delta^{2,4}$-dienol acetate formation.

It has been suggested that acetylium ion can cause hydride abstraction to produce acetaldehyde but the latter was neither isolated nor identified.[29] To determine if hydride abstraction was in fact the oxidative step, the crude reaction mixture was treated with dinitrophenylhydrazine reagent and the product examined by tlc. Acetaldehyde dinitrophenylhydrazone was isolated and its identity was established by mixture melting point with authentic material.

From previous work it has been shown that in an unsubstituted Δ^4-3-ketone such as **1a** there is formation of an intermediate $\Delta^{2,4}$-dienol acetate which is C acylated at the 2 position.[2] When a 2-alkyl substituent is present the formation of $\Delta^{2,4}$-dienol acetate is favored[30,31] but the C-acylation reaction is prohibited.[4] Under these conditions hydride abstraction plays a significant role. The allylically activated hydrogens at C-1 are the most likely candidates for abstraction. Delocalization of the charge in **12** results in an intermediate which is capable of undergoing a dienone–phenol type of rearrangement to give structure **14**.

Further evidence for the stability of the $\Delta^{2,4}$-dienic system in the 2-alkylated steroids may be derived from the arrangement of double bonds in the C-6 acylated products that are formed. In compound **13a** the precursor is probably a methyl ketone **15a** which results from acetylium ion attack on the $\Delta^{3,5}$-dienol acetate **10a**. Enol acetylation of the C-6 acyl compound would be expected to yield 6-acetyl-3,17β-diacetoxyandrosta-3,5-diene.[2] In contrast, the stability of the $\Delta^{2,4}$-diene system is such that the compound undergoes further O acylation to yield the $\Delta^{2,4}$-ethylidene derivative **13a**.[32]

The lack of C-acylation products in the perchloric acid catalyzed enol acetylation of **1i** is in accord with the results obtained by Gorodetsky with similar compounds.[4] In this case, the hyperconjugative effects cancel each other and the $\Delta^{3,5}$-diene **10c** is the most stable product.

The isopropenyl acetate enol acetylation of **1i** is surprising in view of previous results.[2] The Δ^4-3-ketone group usually forms the $\Delta^{3,5}$-dienol acetate; however, with the 2α and 6β substituents a 1:1 mixture of dienol acetates **9d** and **10c** was obtained. When the reaction was carried out with the C-6 epimer **1k** only a single enol acetate **10c** was formed. These results indicate that under the isopropenyl acetate enol acetylation conditions the 6β axial proton is lost more readily than the 6α equatorial proton.[16,33]

Further insight into the behavior of these steroids toward O and C acylation can be derived from the perchloric acid catalyzed enol acetylation of **1e**. In this structure the hyperconjugative effect stabilizes the $\Delta^{3,5}$-dienol acetate **10e** to such an extent that the transient formation of **9e** is forbidden and C-2 acylation does not occur. This contrasts sharply with the behavior of testosterone which under these conditions forms predominantly the C-2 acylation product.[2]

Experimental Section

General.—Melting points were determined on an Electrothermal apparatus by the capillary method and are corrected. Rotations were measured in chloroform solution. The ir spectra were recorded on a Perkin-Elmer Model 237B double-beam spectrophotometer. The uv spectra were determined in ethanol solution using a Bausch and Lomb Spectronic 502 recording spectrophotometer. The nmr spectra were determined on a Varian A-60A spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Hydroxyl proton signals were detected by hydrogen–deuterium exchange with D_2O. The mass spectra were determined on a Hitachi–Perkin-Elmer

(27) O. R. Rodig and G. Zanati, *J. Org. Chem.*, **32**, 1423 (1967).

(28) Under the reaction conditions used the dienone–phenol rearrangement of **11a** was complete in approximately 10 min. The glpc conditions used were such that approximately 0.25% **11a** would have been detected.

(29) (a) G. Baddeley and E. Wrench, *J. Chem. Soc.*, 1324 (1959); (b) G. Baddeley, B. G. Heaton, and J. W. Rasburn, *ibid.*, 4713 (1960).

(30) The hyperconjugative effect is known to be the dominant factor in determining the direction in which an unsymmetrical ketone will enolize under acid conditions.[31]

(31) (a) W. D. Emmons and M. F. Hawthorne, *J. Amer. Chem. Soc.*, **78**, 5593 (1956); (b) H. M. E. Cardwell and A. E. H. Kilmer, *J. Chem. Soc.*, 2430 (1951).

(32) There are two possible geometrical isomers for compound **13**, but only a single product could be detected. An examination of Dreiding models suggested that the isomer with the acetoxyl group on the same side as the C-4 vinylic proton is the more probable.

(33) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).

RMU-6D spectrometer. Gas chromatography was carried out on a Model 810 F & M gas chromatograph equipped with dual flame detectors. The columns were 5% fluorosilicone FS-1265 (QF-1) on 60–80 mesh Diatoport S, 8 ft × 4 mm o.d. The carrier gas was helium at a flow rate of 60 ml/min and the column temperature was 230°. Quantitative estimation of components was made by triangulation of the signals.

17β-Hydroxy-2α-methylandrost-4-en-3-one (1f).—Testosterone (**1a**, 10 g) was dissolved in absolute ethanol (50 ml) and treated with a solution of sodium (2 g) and ethyl oxalate (10 ml) in absolute ethanol (50 ml). The reaction mixture was cooled to 0° and left overnight. The solution was brought to pH 3 with 3 *N* sulfuric acid and the mixture was partitioned between ether (500 ml) and water (1 l.). The organic layer was washed with saturated sodium bicarbonate solution, salt solution, and dried ($MgSO_4$). The crude ethoxyoxalyl derivative (12.6 g) was analyzed by tlc using benzene–ethanol 8:1 and was found to be free of starting material. The oxalyl derivative in acetone (350 ml) was refluxed (24 hr) with a mixture of methyl iodide (50 ml) and anhydrous potassium carbonate (25 g). The solvent was evaporated and the residue partitioned between ether (500 ml) and water (500 ml). The organic layer was dried ($MgSO_4$) and the solvent was evaporated leaving crude 2-methyl-2-ethoxyoxalyl derivative (12.0 g). The product was dissolved in methanol (150 ml) and treated with sodium methoxide (3.5 g) in methanol (65 ml) for 1 hr. The reaction mixture was acidified (pH 5) with acetic acid and the solvent was evaporated to dryness. The residue was crystallized from acetone–ether yielding 17β-hydroxy-2α-methylandrost-4-en-3-one (**1f**, 8.3 g): mp 155–158°; $[\alpha]^{26}D$ +108° (c 1.0) (lit.[5] mp 149–153°).

17β-Acetoxy-2α-methylandrost-4-en-3-one (1c).—Acetylation of 17β-hydroxy-2α-methylandrost-4-en-3-one (**1f**, 1 g) by the usual method using pyridine–acetic anhydride afforded the 17β-acetate **1c** which was crystallized from acetone–hexane (860 mg): mp 179–180°; $[\alpha]^{26}D$ +96.5° (*c* 1.0); uv max 240 mμ (ε 14,500); ir (CCl_4) 1675 (C=O), 1623 (C=C), 1740 cm^{-1} (ester C=O).

Anal.[34] Calcd for $C_{22}H_{32}O_3$: C, 76.64; H, 9.50. Found: C, 76.36; H, 9.34.

17β-Hydroxy-2α-ethylandrost-4-en-3-one (1g).—The ethoxalylation of testosterone (**1a**, 10 g) was carried out as previously described. The alkylation procedure was carried out with ethyl iodide (80 ml) using an extended reflux of 80 hr. The crude product **1g** (2.3 g) was purified by column chromatography over Florisil (120 g) and the product was eluted with benzene–hexane 19:1. Crystallization from acetone–hexane gave **1g** (960 mg): mp 112–113°; $[\alpha]^{26}D$ +118° (*c* 1.0); uv max 241 mμ (ε 14,800); ir (CCl_4) 1675 (C=O), 1625 cm^{-1} (C=C); nmr δ 0.80 (s, 3, 18-H_3), 1.21 (s, 3, 19-H_3), 1.03 (t, 3, *J* = 6.5 Hz, 2-CH_2CH_3), 5.70 (s, 1, 4-H).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.59; H, 10.38.

17β-Acetoxy-2α-ethylandrost-4-en-3-one (1d).—Acetylation of 17β-hydroxy-2α-ethylandrost-4-en-3-one (**1g**, 900 mg) using pyridine–acetic anhydride gave the corresponding 17β-acetate **1d**, which crystallized from acetone–hexane (800 mg): mp 135–137°; $[\alpha]^{26}D$ +76.5 (*c* 1.1); uv max 240 mμ (ε 14,500); ir (CCl_4) 1740 (ester C=O), 1680 (C=O), 1627 cm^{-1} (C=C).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.01; H, 9.68.

3,3-Ethylenedioxy-2α-methylandrost-5-en-17β-ol (2).—A solution of 17β-hydroxy-2α-methylandrost-4-en-3-one (**1f**, 4.25 g) in ethylene glycol (215 ml) containing *p*-toluenesulfonic acid (425 mg) was distilled slowly (4 hr) *in vacuo* to half-volume, the bath temperature being kept below 90°. The reaction mixture was cooled and poured into 1% aqueous pyridine (1 l.) and stirred for 15 min. The suspension was filtered and the solid was washed with water. The crude product **2** (3.6 g) was dried under vacuum and recrystallized from acetone–hexane (3 g): mp 176–178°; $[\alpha]^{29}D$ −8.3° (*c* 1.0); ir (CCl_4) 3500 and 3625 (OH), 1668 (C=C), 1090 and 1046 cm^{-1} (ketal); nmr δ 0.76 (s, 3, 18-H_3), 1.06 (s, 3, 19-H_3), 0.86 (d, 3, *J* = 6.5 Hz, 2-CH_3), 3.65 (m, 1, 17-**H**), 3.95 [s, 4, $(CH_2)_2O_2C$-3], 5.26 (m, 1, 6-H).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.82; H, 9.93.

3,3-Ethylenedioxy-5α,6α-epoxy-2α-methylandrostan-17β-ol (3).—To a chilled solution of 3,3-ethylenedioxy-2α-methylandrost-5-en-17β-ol (**2**, 23 g) in anhydrous benzene (890 ml) was added a chilled solution of *m*-chloroperbenzoic acid (13.2 g) in chloroform (50 ml). The solution was stored at 8° and the crude product monitored by glpc analysis. The latter demonstrated that 50 hr was the optimum reaction time. The analysis indicated that there was formed 30% 5β,6β-epoxide **4** and 70% 5α,6α-epoxide **3**. The reaction mixture was washed with bicarbonate solution (150 ml) and sodium chloride solution until neutral and dried (Na_2SO_4). The solvent was removed and the product chromatographed over Florisil (250 g). Elution with benzene removed the 5β,6β-epoxide along with some hydrolyzed ketal. Further elution of the column with benzene–ether 9:1 gave 3,3-ethylenedioxy-5α,6α-epoxy-2α-methylandrostan-17β-ol (**3**, 5.7 g): mp 224–226°; $[\alpha]^{28}D$ −20.3° (*c* 1.1); ir (CCl_4) 3620 (OH), 1090, 1045 and 1023 cm^{-1} (ketal); nmr δ 0.72 (s, 3, 18-H_3), 0.94 (d, 3, *J* = 6.5 Hz, 2-CH_3), 1.11 (s, 3, 19-H_3), 2.78 (d, 1, *J* = 4 Hz, 6-H).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.22; H, 9.23.

3,3-Ethylenedioxy-5β,6β-epoxy-2α-methylandrostan-17β-ol (4).—The crude mixture of epoxide **4** and hydrolyzed starting material **1f** isolated from the above column was crystallized from acetone–1% pyridine. The analytical specimen of **4** had mp 216–217.5°; $[\alpha]^{28}D$ −1.4° (*c* 1.1); ir (CCl_4) 3620 (OH), 1090 and 1050 cm^{-1} (ketal); nmr δ 0.73 (s, 3, 18-H_3), 0.87 (d, 3, *J* = 6 Hz, 2-CH_3), 1.06 (s, 3, 19-H_3), 3.03 (d, 1, *J* = 2.5 Hz, 6-H), 3.92 [s, 4, $(CH_2)_2O_2C$-3].

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.18; H, 9.61.

3,3-Ethylenedioxy-2α,6β-dimethylandrostane-5α,17β-diol (5a).—To anhydrous ether (10 ml) was added ether-washed magnesium turnings (470 mg) and methyl iodide (1.3 ml). The mixture was refluxed under nitrogen until dissolution of the metal was complete. A solution of 3,3-ethylenedioxy-5α,6α-epoxy-2α-methylandrostan-17β-ol (**3**, 1.04 g) in tetrahydrofuran (100 ml) was added and refluxed for 78 hr. The reaction was quenched by addition of saturated NH_4Cl solution until all of the salts dissolved. The supernatant liquid was decanted and the aqueous portion washed with dichloromethane (200 ml). The organic portions were combined, and evaporated to dryness. The residue was partitioned between methylene chloride (100 ml) and brine (100 ml), dried (Na_2SO_4), and the solvent evaporated leaving crude material (940 mg). Recrystallization from acetone–hexane gave **5a** (835 mg): mp 225–226°; $[\alpha]^{28}D$ −15.2° (*c* 0.98); ir (CCl_4) 3630, 3520 (OH), 1090, and 1048 cm^{-1} (ketal). The compound was homogeneous by glpc analysis.

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.11. Found: C, 72.04; H, 10.07.

5α,17β-Dihydroxy-2α,6β-dimethylandrostan-3-one (5b).—A solution of 3,3-ethylenedioxy-2α,6β-dimethylandrostane-5α,17β-diol (56 mg) in 75% acetic acid (6 ml) was heated on a steam bath for 45 min and the solvents removed under vacuum. The residue was dissolved in ether (25 ml) and washed with sodium bicarbonate solution and brine. The solution was dried (Na_2SO_4), the solvent removed, and the residue crystallized from acetone–hexane to yield **5b** (33 mg): mp 112–114° (with decomposition); $[\alpha]^{27}D$ −7.9° (*c* 0.7); ir (CCl_4) 3640 (OH), 1715 cm^{-1} (C=O); nmr δ 0.78 (s, 3, 18-H_3), 1.30 (d, 3, *J* = 6.5 Hz, $CHCH_3$), and 1.07 (d, 3, *J* = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.32; H, 10.42.

17β-Hydroxy-2α,6β-dimethylandrost-4-en-3-one (1h).—A solution of 5α,17β-dihydroxy-2α,6β-dimethylandrostan-3-one (400 mg) in 50% aqueous methanolic sodium hydroxide solution (76 ml of 0.05 *N*) was stirred at room temperature under nitrogen for 17 hr. Acetic acid (4 ml) was then added and the mixture concentrated to half-volume. The reaction product was extracted with ether (150 ml), washed with brine, and dried (Na_2SO_4). The solvent was removed and the residue was crystallized from acetone–hexane to yield **1h** (200 mg): mp 190–191°; $[\alpha]^{28}D$ 56.8° (*c* 1.0); uv max 241 mμ (ε 15,500); ir (CCl_4) 3620 (OH), 1680 (C=O) 1615 cm^{-1} (C=C); nmr δ 0.81 (s, 3, 18-H_3), 1.09 (d, 3, *J* = 7 Hz, $CHCH_3$), 1.21 (d, 3, *J* = 8 Hz, $CHCH_3$), 1.28 (s, 3, 19-H_3), and 4.75 (s, 1, 4-H).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.62; H, 10.32.

17β-Acetoxy-2α,6α-dimethylandrost-4-en-3-one (1k).—To a solution of 17β-hydroxy-2α,6β-dimethylandrost-4-en-3-one (**1h**, 64 mg) in benzene (10 ml) was added *p*-toluenesulfonic acid (15 mg) and the solution was refluxed until glpc analysis indicated

(34) Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

complete conversion (3.5 hr) to the isomeric 17β-hydroxy-2α,6α-dimethylandrost-4-en-3-one (**1j**). The solution was poured into sodium bicarbonate solution (20 ml) and the organic layer was washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residual oil (54 mg), homogeneous by glpc and tlc, failed to crystallize. The nmr spectrum ($CDCl_3$) showed δ 0.80 (s, 3, 18-H_3), 1.05, 1.12, 1.16, 1.23, and 1.26 (a series of methyl signals in which assignments could not be made), 5.80 (d, 1, J = 2 Hz, 4-H). The compound was acetylated using pyridine–acetic anhydride reagent and the corresponding acetate **1k** failed to crystallize from the usual solvents: $[\alpha]^{28}D$ +62.5° (*c* 0.5); ir (CCl_4) 1731 (ester), 1668 (C=O), and 1618 cm^{-1} (C=C).

6-Methylpregn-5-ene-3β,17α,20ξ-triol.—3β,17α-Dihydroxy-6-methylpregn-5-en-20-one (**6**, 10.046 g) in absolute ethanol (500 ml) was treated with sodium borohydride (12.2 g), and the reactants were refluxed with stirring for 3.5 hr. The mixture was evaporated to dryness under reduced pressure, and the residue was extracted with dichloromethane. The organic solution was washed with brine and dried (Na_2SO_4), and the solvent was evaporated. The residue (9.7 g), a mixture of C-20 epimeric compounds, had no absorption in the carbonyl region of the infrared spectrum, and was not purified further but used directly in the next experiment.

3β-Hydroxy-6-methylandrost-5-en-17-one (**7**).—Sodium periodate (11.3 g) in water (100 ml) was added dropwise with stirring to an ice-cold solution of 6-methylpregn-5-ene-3β,17α,20ξ-triol (9.7 g) in ethanol (300 ml). When the addition was complete the ice bath was removed and the mixture was stirred at room temperature for 6 hr. The mixture was poured into ice–water (2 l.) and refrigerated overnight to crystallize. The product (**7**, 5.15 g) was collected by filtration and recrystallized from acetone: mp 146.5–148°; $[\alpha]^{28}D$ +5.6° (*c* 1.2); ir (CCl_4) 3625 (OH), 1740 (C=O) and 1045 cm^{-1}.

Anal. Calcd for $C_{20}H_{30}O_2 \cdot 0.5(CH_3)_2CO$: C, 77.90; H, 10.03. Found: C, 78.07; H, 10.03.

6-Methylandrost-5-en-3β-ol (**8**).—3-Hydroxy-6-methylandrost-5-en-17-one (6.4 g) in diethylene glycol (250 mg) was treated with 95% anhydrous hydrazine (50 ml) and potassium hydroxide (20 g). The reactants were refluxed (reflux temperature 155°) for 1.5 hr, and then hydrazine and water were distilled off until the temperature reached 203°. The reaction mixture was refluxed for a further 6 hr at 203°, then cooled to room temperature, and water (1.5 l.) was added. The resulting crystals were filtered off, washed with water, dried at 60°, and recrystallized from acetone–hexane to yield 6-methylandrost-5-en-3β-ol (**8**, 4.96 g): mp 138–139°; $[\alpha]^{29}D$ −34.6° (*c* 1.0); ir (CCl_4) 3625, 1374, 1055 and 1045 cm^{-1}; nmr δ 0.74 (s, 3, 18-H_3), 1.01 (s, 3, 19-H_3), 1.63 (s, 3, 6-CH_3), and 3.70 (s, 1, OH).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.49; H, 11.34.

Oxidation of 6-Methylandrost-5-en-3β-ol (**8**) **with Chromic Oxide–Pyridine Reagent.**—6-Methylandrost-5-en-3β-ol (4.8 g) was added with stirring to a slurry of chromic oxide (7 g) and pyridine (150 ml). The reactants were kept at room temperature overnight, and more chromic oxide (3 g) in pyridine (40 ml) was added. After 40 hr of reaction ether (500 ml) was added and the mixture was filtered through Celite. The residue was washed with ether, and the filtrate and washings were washed with saturated sodium bicarbonate solution, water, 2 *N* hydrochloric acid, brine, and dried (Na_2SO_4). The solvent was evaporated and the residue (3.5 g) was taken up in benzene and adsorbed on to a column of Florisil (200 g). Elution with benzene–ether (9:1) and crystallization of the product from acetone–hexane afforded 6β-hydroxy-6α-methylandrost-4-en-3-one (**16**, 923 mg): mp 211–213.5°; $[\alpha]^{28}D$ +3.3° (*c* 1.2); uv max 239 mμ (ε 8900); ir (CCl_4) 3600 (OH), 1675 cm^{-1} (C=C—C=O); nmr δ 0.80 (s, 3, C_{18}-H_3), 1.42 and shoulder at 1.41 (s, 6, 19-H_3 and 6-$OHCH_3$), 1.60 (s, 1, OH), and 6.01 (s, 1, 4-H); mass spectrum *m/e* (relative intensity) 302 (9), 260 (100), 149 (15), and 135 (16).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.51; H, 10.19.

6α-Methylandrost-4-en-3-one (**1e**).—6-Methylandrost-5-en-3β-ol (**8**, 4.16 g) in dry benzene (100 ml) was treated with aluminum *t*-butoxide (5.5 g) and cyclohexanone (12 ml). The mixture was refluxed for 18 hr and then cooled to room temperature. The reaction mixture was diluted with ether and washed with dilute sulfuric acid, sodium bicarbonate solution, and brine, and then dried (Na_2SO_4). The solvent was evaporated and the residual oil was taken up in hexane and adsorbed onto a column of Florisil (200 g). Elution with hexane removed cyclohexanone and cyclohexanol. Further elution with benzene afforded 6α-methylandrost-4-en-3-one (**1e**, 1.628 g): mp 117–118°; $[\alpha]^{28}D$ +95.5° (*c* 1.1); uv max 241 mμ (ε 14,500); ir (CCl_4) 1675, shoulder at 1680 (C=C-C=O), 1610 (C=C), 1375, and 1265 cm^{-1}; nmr δ 0.77 (s, 3, 18-H_3), and 5.82 (d, 1, J = 1.6 Hz, 4-H).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.94; H, 10.76.

3,17β-Diacetoxy-2α-methylandrosta-3,5-diene (**10a**).—17β-Hydroxy-2α-methylandrost-4-en-3-one (**1f**, 5 g) was suspended in isopropenyl acetate (50 ml) and treated with sulfuric acid (0.02 ml). The solution was refluxed under nitrogen for 2 hr, and then cooled and diluted with ether (200 ml). The ether solution was washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was taken up in benzene and filtered through a short column of Florisil to remove coloration. The filtrate was evaporated and the residue was crystallized from ethanol–1% pyridine to yield 3,17β-diacetoxy-2α-methylandrosta-3,5-diene (**10a**, 3.3 g): mp 169–171°; $[\alpha]^{31}D$ −30° (*c* 1.0); uv max 237 mμ (ε 17,050); ir (CCl_4) 1748 (C=COCOCH$_3$), 1723 (-OCOCH$_3$), 1659 and 1632 cm^{-1} (C=C); nmr δ 0.83 (s, 3, 18-H_3), 0.96 (d, 3, J = 4.5 Hz, 2-CH_3), 1.06 (s, 3, 19-H_3), 2.03 (s, 3, 17-OCOCH$_3$), 2.12 (s, 3, 3-OCOCH$_3$), 5.36 (m, 1, 6-H), and 5.64 (d, 1, J = 2.0 Hz, 4-H).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.56; H, 8.87. Found: C, 74.76; H, 9.04.

3,17β-Diacetoxy-2α-ethylandrosta-3,5-diene (**10b**).—17β-Hydroxy-2α-ethylandrost-4-en-3-one (**1g**, 883 mg) was treated with isopropenyl acetate (10 ml) and sulfuric acid (0.02 ml) as described for the synthesis of compound **10a**. The product was crystallized from acetone–hexane to give 3,17β-diacetoxy-2α-ethylandrosta-3,5-diene (**10b**, 652 mg): mp 219–221°; $[\alpha]^{28}D$ −29.5° (*c* 1.0); uv max 238 mμ (ε 20,250); ir (CCl_4) 1755 and 1220 (C=COCOCH$_3$), 1735 and 1240 (-OCOCH$_3$), and 1175 cm^{-1}; nmr δ 0.83 (s, 3, 18-H_3), 1.03 (s, 3, 19-H_3), 2.02 (s, 3, 17-OCOCH$_3$), 2.12 (s, 3, 3-OCOCH$_3$), 4.63 (m, 1, 17-H), 5.39 (m, 1, 6-H), and 5.67 (d, 1, J = 2.5 Hz, 4-H); mass spectrum *m/e* (relative intensity) 400 (8), 360 (5), 359 (35), 358 (100), 344 (6), 343 (4), and 147 (6).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.20; H, 9.05.

Enol Acetylation of 2α,6β-Dimethyl-17β-hydroxyandrost-4-en-3-one (**1h**) **Using Isopropenyl Acetate. A. *p*-Toluenesulfonic Acid Catalyst.**—2α,6β-Dimethyl-17β-hydroxyandrost-4-en-3-one (**1h**, 187 mg) was treated with isopropenyl acetate (10 ml) and *p*-toluenesulfonic acid (23 mg) and the solution was refluxed under nitrogen. Glpc analysis of aliquots of the reaction mixture indicated that the reaction was complete after 3 hr and that two products were formed in approximately equal amounts with retention times of 6.8 and 7.2 min. The reaction was quenched by partitioning between saturated aqueous sodium bicarbonate and ether. The ether layer was washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was taken up in benzene–hexane (1:1) and adsorbed on to a column of Florisil impregnated with 10% silver nitrate. Elution with benzene–hexane (1:1) afforded 3,17β-diacetoxy-2α,6-dimethylandrosta-3,5-diene (**10c**, 51 mg), which crystallized from aqueous methanol: mp 142–144°; $[\alpha]^{27.5}D$ −64.5° (c 0.5); uv max 247 mμ (ε 21,467); ir (CCl_4) 1760 and 1225 (>C=COCOCH$_3$), 1740 and 1245 (-OCOCH$_3$), 1660 and 1630 (diene), and 1195 cm^{-1}; nmr δ 0.83 (s, 3, 18-H_3), 0.97 (d, 3, J = 6.4 Hz, 2-CH_3), 1.03 (s, 3, 19-H_3), 1.62 (s, 3, 6-CH_3), 2.04 (s, 3, 17-OCOCH$_3$), 2.16 (s, 3, 3-OCOCH$_3$), 4.65 (m, 1, 17-H), and 6.04 (d, 1, J = 2 Hz, 4-H).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.85; H, 9.07.

Further elution with benzene yielded 3,17β-diacetoxy-2,6β-dimethylandrosta-2,4-diene (**9d**, 48 mg) which was crystallized from acetone–hexane: mp 154–156°; $[\alpha]^{28.5}D$ +167.3° (*c* 1.0); uv max 269 mμ (ε 10,760); ir (CCl_4) 1760 and 1230 (C=COCOCH$_3$), 1740 and 1245 (-OCOCH$_3$), 1680 (C=C), 1375 and 1124 cm^{-1}; nmr δ 0.83 (s, 3, 18-H_3), 1.03 (s, 3, 19-H_3), 1.15 (d, 3, J = 7.5 Hz, 6-CH_3), 1.60 (s, 3, 2-CH_3), 2.03 (s, 3, 17-OCOCH$_3$), 2.15 (s, 3, 3-OCOCH$_3$), 4.61 (m, 1, 17-H), and 5.38 (s, 1, 4-H).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.64; H, 8.91.

B. Sulfuric Acid Catalyst.—2α,6β-Dimethyl-17β-hydroxyandrost-4-en-3-one (**1h**, 80 mg) in isopropenyl acetate (15 ml) was treated with sulfuric acid (2 drops), and the mixture was refluxed under nitrogen for 2.5 hr. Glpc analysis of aliquots of

the reaction mixture showed that the reaction was complete after 1 hr and that the reaction mixture consisted of 3,17β-diacetoxy-2α,6-dimethylandrosta-3,5-diene (**10c**) and 3,17β-diacetoxy-2,6β-dimethylandrosta-2,4-dinee (**9d**) in the ratio 85:15.

Enol Acetylation of 17β-Acetoxy-2α,6α-dimethylandrost-4-en-3-one (1k).—To a solution of the title compound **1k** (30 mg) in isopropenyl acetate (3 ml) was added *p*-toluenesulfonic acid (5 mg) and the mixture was refluxed under nitrogen until glpc analysis indicated the reaction was complete (3 hr). A single product could be detected by glpc analysis. The product was isolated as previously described. The crude product was filtered through Florisil and eluted with benzene. The product, 3,17β-diacetoxy-2α,6-dimethylandrosta-3,5-diene (**10c**), was crystallized from aqueous methanol (5 mg): mp 136–141°; mixture melting point with authentic material previously prepared was undepressed.

3-Acetoxy-6-methylandrosta-3,5-diene (10e).—6α-Methylandrost-4-en-3-one (**1e**, 263 mg) was treated with isopropenyl acetate (10 ml) and sulfuric acid (0.01 ml) as described for the synthesis of compound **10a**. The product was crystallized from aqueous methanol to yield 3-acetoxy-6-methylandrosta-3,5-diene (**10e**, 185 mg): mp 86–88°; $[\alpha]^{28}D$ −165.6° (*c* 1.2); uv max 245 mμ (ε 15,200); ir (CCl_4) 1755 and 1225 (C=COCOCH₃), 1660 and 1630 cm⁻¹ (diene); nmr δ 0.75 (s, 3, 18-H₃), 0.99 (s, 3, 19-H₃), 1.66 (d, 3, *J* = 0.5 Hz, 6-CH₃), 2.16 (s, 3, 3-OCOCH₃), and 6.13 (d, 1, *J* = 2.0 Hz, 4-H).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.62; H, 9.99.

Treatment of 3,17β-Diacetoxy-2α-methylandrosta-3,5-diene (10a) with Perchloric Acid–Acetic Anhydride Reagent.—3,17β-Diacetoxy-2α-methylandrosta-3,5-diene (**10a**, 1.25 g) in benzene (200 ml) and carbon tetrachloride (80 ml) was treated with a solution (50 ml) of 70% perchloric acid (0.5 ml) in acetic anhydride (249.5 ml) at room temperature. Glpc analysis of aliquots of the reaction mixture indicated that the reaction was complete after 6 hr, and showed that the products were **14a** (22%, retention time 10.5 min) and **13a** (77.2%, retention time 26.0 min). The reaction was quenched by dilution with sodium bicarbonate solution (100 ml) and ether (100 ml). The organic layer was washed with bicarbonate solution and brine, dried (Na_2SO_4), and the solvent was evaporated. The residue (2.3 g of dark material) was taken up in benzene–hexane (4:1) and adsorbed on to a column of Florisil (200 g). Elution with benzene–ether (200:1) yielded 1,17β-diacetoxy-2,4-dimethylestra-1,3,5(10)-triene (**14a**, 29 mg): mp 184–185.5°; the mixture melting point with authentic compound was undepressed. The mass spectrum had a molecular ion peak at *m/e* 384. Saponification of the acetate groups with alcoholic potassium hydroxide by the usual method yielded 2,4-dimethylestra-1,3,5(10)-triene-1,17β-diol (**14c**): mp 164–166°; the mixture melting point with authentic material was undepressed.

Further elution of the column with benzene–ether (50:1) afforded 6-(1′-acetoxyethylidene)-3,17β-diacetoxy-2-methylandrosta-2,4-diene (**13a**, 120 mg) which was crystallized from ethanol: mp 167–168°; $[\alpha]^{28}D$ +446° (c 1.0); uv max 288 mμ (ε 9400); ir (CCl_4) 1750 (C=COCOCH₃), 1735 (–OCOCH₃) and 1680 cm⁻¹ (C=C); nmr δ 0.8 (s, 3, 18-H₃), 0.95 (s, 3, 19-H₃), 1.64 (s, 3, 2-CH₃), 2.00 (s, 3), 2.02 (s, 3), 2.12 (s, 3), 2.15 (s, 3), 4.63 (m, 1, 17-H), and 5.42 (s, 1, 4-H); molecular weight by mass spectrometry 470.

Anal. Calcd for $C_{28}H_{38}O_6$: C, 71.46; H, 8.14. Found: C, 71.37; H, 8.09.

6-(1′-Acetoxyethylidene)-3,17β-diacetoxy-2-ethylandrosta-2,4-diene (13b). **A.**—To a stirred solution of 3,17β-diacetoxy-2α-ethylandrosta-3,5-diene (190 mg) in dry benzene (25 ml) and carbon tetrachloride (10 ml) was added a solution (6.4 ml) prepared from acetic anhydride (249.5 ml) and 70% perchloric acid (0.5 ml). Glpc analysis of aliquots of reaction mixture indicated that the reaction was complete after 75 min and that two products were formed. The major constituent (90%) was 6-(1′-acetoxyethylidene)-3,17β-diacetoxy-2-ethylandrosta-2,4-diene (**13b**) and the minor component (10%) was 1,17β-diacetoxy-2-ethyl-4-methylestra-1,3,5(10)-triene (**14b**) whose isolation is described subsequently. The reaction mixture was diluted with ether and washed with saturated sodium bicarbonate solution and water, dried (Na_2SO_4), and the solvent was evaporated. The residue was taken up in benzene–hexane (1:1) and adsorbed on to a column of Florisil (20 g). Elution with benzene–ether (19:1) afforded **13b** (84 mg), which was crystallized from acetone–hexane: mp 184–187°; $[\alpha]^{27.5}D$ +321.3° (*c* 0.3); uv max 293 mμ (ε 10,920); ir (CCl_4) 1755 and 1220 (C=COCOCH₃), 1740 and 1240 cm⁻¹ (–OCOCH₃); nmr δ 0.80 (s, 3, 18-H₃), 0.95 (s, 3, 19-H₃), 0.96 (t, 3, *J* = 7 Hz, 2-CH_2CH_3),[35] 1.98 (s, 3), 2.01 (s, 3), 2.12 (s, 3), 2.15 (s, 3), 4.60 (m, 1, 17-H), and 5.42 (s, 1, 4-H); mass spectrum *m/e* (relative intensity) 484 (11), 443 (31), 442 (100), 401 (19), 400 (68) and 121 (31).

Anal. Calcd for $C_{29}H_{40}O_6$: C, 71.87; H, 8.32. Found: C, 71.91; H, 7.98.

B.—2α-Ethyltestosterone (**1g**, 582 mg) was treated in a manner analogous to the above, and after crystallization from acetone–hexane 226 mg of compound **13b** was obtained, identical in every respect with the material obtained from the above experiment.

Isolation of 1,17β-Diacetoxy-2-ethyl-4-methylestra-1,3,5(10)-triene (14b) from the Reaction of 2α-Ethyltestosterone with Perchloric Acid–Acetic Anhydride Reagent.—2α-Ethyltestosterone (**1b**, 367 mg) in benzene (50 ml) and carbon tetrachloride (20 ml) was treated with a solution (5 ml) prepared from 70% perchloric acid (5 ml) and acetic anhydride (245 mg). The mixture was stirred at room temperature for 3 hr. Glpc analysis of aliquots of reaction mixture indicated that reaction was complete, and that two products were formed in approximately a 9:1 ratio. The isolation of the major constituent, compound **13b**, is described above. The isolation of the minor component was achieved by dilution with ether, washing with saturated sodium bicarbonate solution and brine, and drying (Na_2SO_4). The solvent was evaporated, and the residue was taken up in methanol (100 ml) and treated with saturated aqueous sodium acetate (20 ml). The solution was refluxed for 3 hr and then evaporated to dryness. The solid material was extracted with ether, and the solvent was evaporated. The residue was taken up in benzene and adsorbed onto a column of Florisil (30 g). Elution with benzene gave 1,17β-diacetoxy-2-ethyl-4-methylestra-1,3,5(10)-triene (**14b**, 27 mg) which crystallized from acetone–hexane, mp 183–186°. Admixture with authentic material gave no depression of the melting point.

Treatment of 2α,6β-Dimethyl-17β-hydroxyandrost-4-en-3-one (1h) with Perchloric Acid–Acetic Anhydride Reagent.—2α,6β-Dimethyl-17β-hydroxyandrost-4-en-3-one (**1h**, 5 mg) in dry benzene (0.5 ml) and carbon tetrachloride (0.2 ml) was treated with a solution (0.05 ml) prepared from 70% perchloric acid (5 ml) and acetic anhydride (245 ml). The solution was stirred at room temperature, and the reaction was monitored by glpc which demonstrated that only one product was formed. The reaction was complete after 1 min and there was no change after a further 3 hr. The mixture was diluted with ether, washed with aqueous sodium bicarbonate and brine, and dried (Na_2SO_4). The ether was evaporated and the product had ir and uv spectra and glpc retention time identical with those of authentic 3,17β-diacetoxy-2α,6-dimethylandrosta-3,5-diene (**10c**).

Treatment of 6α-Methylandrost-4-en-3-one (1e) with Perchloric Acid–Acetic Anhydride Reagent.—6α-Methylandrost-4-en-3-one (**1e**, 196 mg) in dry benzene (25 ml) and carbon tetrachloride (10 ml) was treated with a solution (7 ml) prepared from acetic anhydride (250 ml) and 70% perchloric acid (0.5 ml) at room temperature. Glpc analysis of aliquots of the reaction mixture indicated that the reaction was complete after 15 min and that there was no further change after 5 hr when the reaction was quenched by partitioning between saturated aqueous sodium bicarbonate and ether. The ether layer was washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was taken up in benzene and filtered through a short column of Florisil to remove coloration. The solvent was evaporated and the residue was crystallized from aqueous methanol to yield 3-acetoxy-6-methylandrosta-3,5-diene (**10e**, 102 mg): mp 86–88°; mixture melting point with authentic material previously prepared was undepressed, and their ir spectra were also identical.

Hydrolysis of 6-(1′-Acetoxyethylidene)-3,17β-diacetoxy-2-methylandrosta-2,4-diene (13a).—The title compound (100 mg) in ethanol (25 ml) was treated with saturated aqueous sodium acetate (5 ml). The mixture was refluxed for 2 hr, and evaporated to dryness. The residue was partitioned between ether (50 ml) and water (50 ml). The ether layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was taken up in benzene and adsorbed onto a column of Florisil (15 g). Elution with benzene gave a mixture with 17β-acetoxy-6β-acetyl-2α-methyl-

(35) The assignment of this signal was verified by spin-decoupling experiments.

androst-4-en-3-one (**15a**) as the major component. Crystallization from acetone–hexane afforded **15a** (8 mg): mp 189–190°; uv max 246 mμ (ε 12,300); uv max (EtOH–5% KOH) 428 mμ (ε 10,800); ir (KBr) 1738 (-OCOCH$_3$), 1725 (C=O), 1685 (C=C–C=O) and 1610 cm^{-1} (C=C);

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.24; H, 8.69.

Hydrolysis of 6-(1′-Acetoxyethylidene)-3,17β-diacetoxy-2-ethylandrosta-2,4-diene (13b).—Compound **13b** (199 mg) in methanol (55 ml) was treated with saturated aqueous sodium acetate (10 ml) and the solution was refluxed for 3 hr. The mixture was evaporated to small volume and extracted with dichloromethane. The organic solution was washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was crystallized from acetone–hexane giving a mixture of C-6 epimers of 17β-acetoxy-6ξ-acetyl-2α-ethylandrost-4-en-3-one (29 mg): uv max 241 mμ (ε 13,500); uv max (EtOH–5% KOH) 425 mμ; ir (CCl_4) 1740 and 1240 (-OCOCH$_3$), 1718 (-COCH$_3$), 1680 and 1612 (O=C–C=C), and 1040 cm^{-1}; nmr δ 0.83 (s, 3, 19-H$_3$), 1.06 and 1.28 (two s, 3, 19-H$_3$ in the two epimers), 2.02 (s, 3, -OCOCH$_3$), 2.12 and 2.18 (two s, 3, epimeric 6-COCH$_3$), 3.23 (d, 1, J = 5 Hz, 6-H), 5.43 (d, 1, J = 1.6 Hz, 4-H in 6α epimer), and 6.03 (s, 1, 4-H in 6β epimer).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.23; H, 9.20.

17β-Hydroxy-2-methylandrosta-1,4-dien-3-one (11a).—A solution of 17β-hydroxy-2α-methylandrost-4-en-3-one (**1f**, 3.07 g) in *t*-butyl alcohol (100 ml) was added to a solution of selenium dioxide (3.07 g) in acetic acid (2.7 ml) and the reaction mixture was refluxed under nitrogen for 75 hr. The mixture was cooled, diluted with ethyl acetate (200 ml), and filtered through Celite. The solvent was evaporated to dryness and the residue was taken up in ethyl acetate (100 ml). The organic solution was washed with three successive portions of water (100 ml), aqueous sodium bicarbonate, cold ammonium sulfide solution (100 ml), cold 3 *N* ammonium hydroxide (100 ml), 3 *N* hydrochloric acid (100 ml), and brine until neutral. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue (2 g) was chromatographed on Florisil (60 g) and eluted with benzene. The product was crystallized from acetone–hexane to yield 17β-hydroxy-2-methylandrosta-1,4-dien-3-one (**11a**, 1.2 g): mp 208–211°; $[\alpha]^{27}D$ +5.8° (*c* 1.0) (lit.[25] mp 210–211°; $[\alpha]D$ +6°).

17β-Acetoxy-2-methylandrosta-1,4-dien-3-one (11b).—17β-Hydroxy-2-methylandrosta-1,4-dien-3-one (**11a**, 500 mg) was acetylated by the usual method using acetic anhydride and pyridine. The product was crystallized from acetone–hexane to yield 17β-acetoxy-2-methylandrosta-1,4-dien-3-one (**11b**, 480 mg): mp 180–182°; $[\alpha]^{26}D$ +7.6° (*c* 1.0); uv max 247 mμ (ε 16,300); ir (CCl_4) 1741 and 1247 (OCOCH$_3$), 1670 (C=C–C=O), 1646, 1633 cm^{-1} (C=C).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.01; H, 8.96.

17β-Acetoxy-2-ethylandrosta-1,4-dien-3-one (11c).—17β-Hydroxy-2α-ethylandrost-4-en-3-one (**1g**, 1.052 g) in *t*-butyl alcohol (30 ml) was treated with selenium dioxide (1.2 g) in acetic acid (10 ml), and the mixture was refluxed under nitrogen for 72 hr. The product was isolated in a manner analogous to that used for compound **11a** and there was obtained by crystallization from acetone–hexane 17β-acetoxy-2-ethylandrosta-1,4-dien-3-one (**11c**, 228 mg): mp 153–154°; $[\alpha]^{29}D$ +9.2° (*c* 1.0); uv max 248 mμ (ε 15,300); ir (KBr) 1735 and 1245 (-OCOCH$_3$), 1665 (C=C–C=O), and 1630 cm^{-1} (C=C); nmr δ 0.87 (s, 3, 18-H$_3$), 1.19 (s, 3, 19-H$_3$), 1.05 (t, 3, J = 7 Hz, 2-CH$_2$CH$_3$), 2.01 (s, 3, 17-OCOCH$_3$), 4.60 (m, 1, 17-H), 6.04 (s, 1, 4-H), and 6.73 (t, 1, J = 1.3 Hz, 1-H).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.57; H, 9.22.

1,17β-Diacetoxy-2,4-dimethylestra-1,3,5(10)-triene (14a).—17β-Acetoxy-2-methylandrosta-1,4-dien-3-one (**11b**, 314 mg) in acetic anhydride (6.0 ml) was treated with *p*-toluenesulfonic acid (120 mg) and the mixture was heated at 90° for 6 hr under nitrogen. The solution was cooled and partitioned between ether (100 ml) and water (50 ml). The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was sublimed at 90° *in vacuo* yielding 1,17β-diacetoxy-2,4-dimethylestra-1,3,5-(10)-triene (**14a**, 195 mg): mp 185–187°; $[\alpha]^{27}D$ +142.5° (*c* 1.0); uv max 272 mμ (ε 4600); ir (CCl_4) 1755 (C=COCOCH$_3$) and 1736 cm^{-1} (-OCOCH$_3$); nmr δ 0.87 (s, 3, 18-H$_3$), 2.04 (s, 3), 2.07 (s, 3) and 2.16 (s, 3) (two aromatic methyl signals and 17-OCOCH$_3$), 2.26 (s, 3, 1-OCOCH$_3$), 4.73 (m, 1, 17-H), and 6.86 (m, 1, aromatic H).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.94; H, 8.39. Found: C, 74.74; H, 8.30.

1,17β-Diacetoxy-2-ethyl-4-methylestra-1,3,5(10)-triene (14b).—To a solution of 17β-acetoxy-2-ethylandrosta-1,4-dien-3-one (**11c**, 68 mg) in dry benzene (10 ml) and carbon tetrachloride (4 ml) was added a solution (2.4 ml) prepared from acetic anhydride (36 ml) and 70% perchloric acid (0.12 ml). The mixture was stirred at room temperature for 40 min and then diluted with ether. The ether solution was washed with saturated sodium bicarbonate solution and brine, dried (Na_2SO_4), and the solvent was evaporated. The residual oil was crystallized from acetone–hexane and afforded 1,17β-diacetoxy-2-ethyl-4-methylestra-1,3,5(10)-triene (**14b**, 45 mg): mp 181–184°; $[\alpha]^{28}D$ +116° (*c* 1.0); ir (CCl_4) 1760 and 1190 (C=COCOCH$_3$), 1735 and 1240 cm^{-1} (OCOCH$_3$); nmr δ 0.85 (s, 3, 18-H$_3$), 1.15 (t, 3, J = 7.8 Hz, 2-CH$_2$CH$_3$), 2.03 (s, 3, 17-OCOCH$_3$), 2.18 (d, 3, J = 1.5 Hz, 4-CH$_3$), 2.27 (s, 3, 1-OCOCH$_3$), 2.48 (q, 2, J = 7.5 Hz, 2-CH$_2$CH$_3$), 4.7 (m, 1, 17-H) and 6.91 (m, 1, 3-H).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.06; H, 8.59.

Detection of Acetaldehyde as a Product of the Reaction of 2α-Methyltestosterone with Perchloric Acid–Acetic Anhydride Reagent.—2α-Methyltestosterone (1.0 g) dissolved in anhydrous benzene (100 ml) and carbon tetrachloride (40 ml) was treated with a solution (10 ml) prepared from acetic anhydride (245 ml) and 70% perchloric acid (5 ml). The mixture was stirred at room temperature for 4 hr and then cooled. A 30-ml sample of the reaction mixture was added to a solution of 2,4-dinitrophenylhydrazine (1.0 g) in methanol (30 ml) containing sulfuric acid (1 ml), and the resulting solution was allowed to stand for 0.5 hr. It was then diluted with chloroform (100 ml), washed with saturated aqueous sodium bicarbonate and brine, and dried (Na_2SO_4). The solvent was evaporated and the residue was taken up in benzene and adsorbed onto a column of neutral alumina (25 g). The column was eluted with benzene, and the orange product was further purified by tlc on silica gel plates (0.5 mm) using benzene as solvent. The band at R_f 0.35 was removed and extracted with dichloromethane. The solvent was evaporated leaving acetaldehyde 2,4-dinitrophenylhydrazone (10 mg) which crystallized from ethanol: mp 147–148°; and the mixture melting point with authentic substance was undepressed.

A "blank" reaction was carried out in the same manner as described above except that the steroid was not included, and no acetaldehyde could be detected.

Registry No.—**1c**, 19990-39-7; **1d**, 19990-40-0; **1e**, 19990-41-1; **1g**, 19990-42-2; **1h**, 19990-43-3; **1k**, 19990-44-4; **2**, 19990-45-5; **3**, 19990-46-6; **4**, 19990-47-7; **5a**, 19990-48-8; **5b**, 19990-49-9; **7**, 298-66-8; **8**, 19990-51-3; **9d**, 19990-52-4; **10a**, 19990-53-5; **10b**, 19990-54-6; **10c**, 19990-55-7; **10e**, 19990-56-8; **11b**, 6223-99-0; **11c**, 19990-58-0; **13a**, 20013-28-9; **13b**, 19990-59-1; **14a**, 6224-21-1; **14b**, 19990-60-4; **15a**, 19990-61-5; **16**, 19990-62-6.

Acknowledgment.—The authors wish to thank Dr. G. A. Neville for the determination of nmr spectra, Dr. P. Morand (University of Ottawa) for the determination of the mass spectra, and Mr. A. Viau for technical assistance.

The Preparation of AB-Dinor Steroids[1]

WILLIAM G. DAUBEN, DAVID J. ELLIS,[2] AND WILLIAM H. TEMPLETON

University of California, Berkeley, California 94720

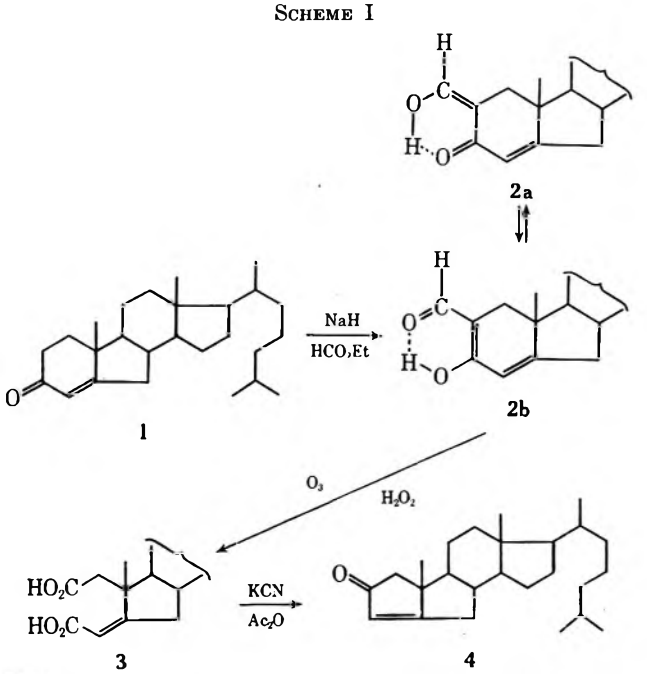
Received November 12, 1968

AB-Dinorcholestenone (4) and AB-dinortestosterone (21) have been synthesized to determine the chemical and biological consequences of contracting both the A and B rings of the steroid nucleus. The AB-dinor analogs were prepared from the corresponding B-nor steroids by formylation of B-norenone 1, ozonization of 2-hydroxymethylene ketone 2, and cyclization of the resulting diacid 3. Catalytic or chemical reduction of enone 4 gave exclusively the 5β-saturated ketone 7. Hydride reduction of *cis* ketone 7 gave predominantly 2α alcohol 12, whereas lithium–ammonia reduction of 7 gave mostly the more stable 2β alcohol 13.

An increasing number of ring-contracted steroids[3] have been reported to possess antihormonal activity.[4] At least one nor steroid, 17α-methyl-B-nortestosterone, has been used clinically as an antiandrogen.[5] It was therefore of considerable interest to see if antihormonal activity could be enhanced by further deviation from the normal steroid nucleus. Accordingly, our previous studies related to the A-nor[6] and B-nor steroids[7] have been extended to the AB-dinor steroids.

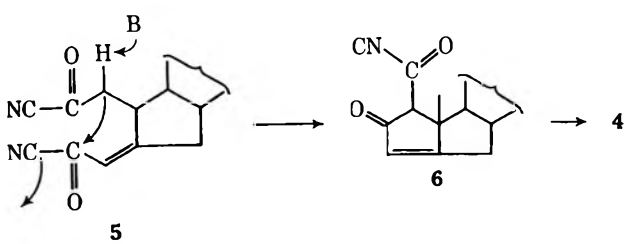
For initial chemical studies, cholesterol was transformed to an AB-dinor analog. The previously reported B-norcholestenone (1)[7] upon reaction with ethyl formate and sodium hydride gave an 85% yield of the 2-hydroxymethylene derivative 2. The infrared (ir) and nuclear magnetic resonance (nmr) spectra of the product showed that it consists of a rapidly equilibrating mixture of the hydroxymethylene form 2a and the formyl tautomer 2b in the approximate ratio 75:25[8] (Scheme I).

SCHEME I



Treatment of 2 with 1 equiv of ozone at −15° resulted in the selective cleavage of the 2,3 bond to give the 2,3-seco diacid 3 in 93% yield after oxidative work-up with hydrogen peroxide.

The key step in the synthesis was the final cyclization of the seco diacid 3. In the synthesis of A-nortestosterone, the corresponding seco diacid was readily cyclized by refluxing in acetic anhydride followed by pyrolysis of the resulting steroidal anhydride.[9] When the B-nor-seco diacid 3 was subjected to these conditions, only a 5% yield of the desired AB-dinorcholestenone (4) was obtained. Pyrolysis of the intramolecular lead salt of 3 gave only a 20% yield of 4.[10] The cyclization was eventually effected in 50–60% yield by refluxing the seco diacid 3 in acetic anhydride containing potassium cyanide.[11] Substitution of potassium acetate or pyridine for potassium cyanide resulted in decreased yields of 4. The cyanide is probably acting as a carbonyl-activating group by the formation of the acyl cyanide 5, which can then undergo base-catalyzed cyclization. The β-keto acyl cyanide 6 can then be converted into 4, either under the reaction conditions or during work-up. The spectral properties of 4 fully confirmed its assigned structure.



The enone 4 was subjected to a variety of reactions to learn more about the chemical behavior of the AB-dinor ring system. Hydrogenation of 4 over palladium on charcoal resulted in the rapid uptake of 1 equiv of hydrogen to give the saturated ketone 7. The existence of more than one isomer could not be demonstrated and the product was assumed to be homogeneous. The 5β configuration would be expected since hydrogenation of either A-nor-[6a,12] or B-norcholestenones (1)[7] yields the 5β-saturated ketones.

(1) This work was supported in part by Grant No. CY-04284, National Cancer Institute, U. S. Public Health Service.

(2) National Science Foundation Graduate Fellow, 1961–1964.

(3) For a comprehensive review of ring contractions of steroids, see B. G. McFarland in "Steroids Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, pp 427–455.

(4) R. I. Dorfman, J. Fajkos, and J. Joska, *Steroids*, **3**, 675 (1964); (b) H. L. Saunders, K. Holden, and J. F. Kerwin, *ibid.*, **3**, 687 (1964); (c) A. Segaloff and R. B. Gabbard, *ibid.*, **4**, 433 (1964); (d) S. M. Kupchan and S. D. Levine, *J. Amer. Chem. Soc.*, **86**, 701 (1964); (e) L. J. Lerner, A. Bianchi, and M. Dzelzkalns, *Acta Endocrinol.*, **44**, 398 (1963); (f) L. J. Lerner, A. V. Bianchi, and M. Dzelzkalns, *Steroids*, **6**, 215, 223 (1965).

(5) A. Zarate, V. B. Mahesh, and R. B. Greenblatt, *J. Clin. Endocrinol. Metab.*, **26**, 1394 (1966).

(6) (a) W. G. Dauben and G. A. Boswell, Jr., *J. Amer. Chem. Soc.*, **83**, 5003 (1961); (b) W. G. Dauben, G. A. Boswell, Jr., and W. H. Templeton, *ibid.*, **83**, 5006 (1961), and previous papers cited therein.

(7) W. G. Dauben, G. A. Boswell, Jr., W. H. Templeton, J. W. McFarland, and G. H. Berezin, *ibid.*, **85**, 1672 (1963), and references cited therein.

(8) E. W. Garbisch, Jr., *ibid.*, **87**, 505 (1965).

(9) F. L. Weisenborn and H. E. Applegate, *ibid.*, **81**, 1960 (1959).

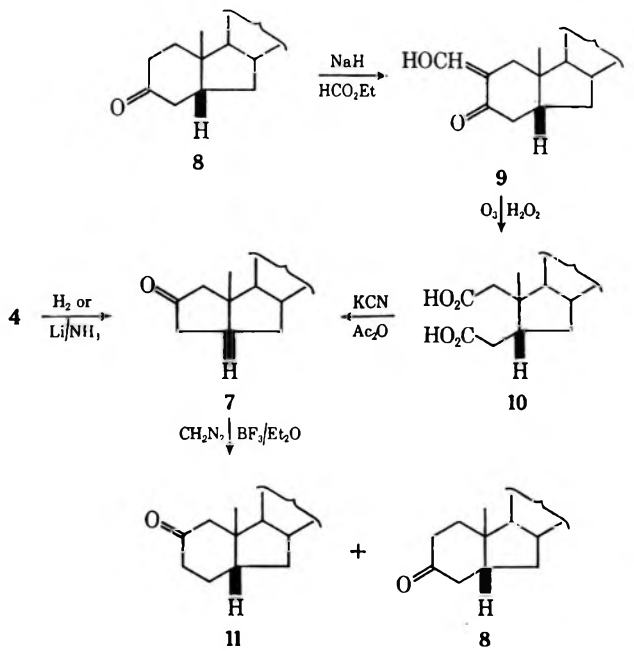
(10) H. Rapoport and J. Pasky, *ibid.*, **78**, 3788 (1956).

(11) F. Uhle, *ibid.*, **71**, 761 (1949).

(12) T. L. Jacobs and N. Takahashi, *ibid.*, **80**, 4865 (1958).

The stereochemistry of hydrogenation was proved by the synthesis of authentic AB-dinor-5β-cholestan-2-one (**7**) from B-nor-5β-cholestan-3-one (**8**) (Scheme II),

SCHEME II



whose C-5 configuration is well established.[7] Treatment of **8** with sodium hydride and ethyl formate gave the 2-hydroxymethylene derivative **9**,[13] which was ozonized to the 2,3-seco diacid **10**. The nmr spectrum of **10** clearly shows that the 2,3 bond had been cleaved, thus, firmly establishing that condensation had occurred at C-2. Cyclization of **10** with acetic anhydride and potassium cyanide gave a 35% yield of AB-dinor-5β-cholestan-2-one (**7**) that was identical with the hydrogenation product of **4**. A similar sequence was carried out with B-nor-5α-cholestan-3-one,[7] but the 5α-seco diacid could not be cyclized to the desired AB-dinor-5α-cholestan-2-one.

Additional chemical evidence for the 5β configuration of **7** was obtained by ring expansion of **7** to the known B-nor-5β ketone **8**. Treatment of **7** with a methylene chloride solution of diazomethane containing a trace of boron trifluoride etherate[14] gave a mixture of B-nor-5β-cholestan-2- and -3-ones (**11** and **8**) in approximately equal amounts. The equal migratory aptitudes of the 1,2 and 2,3 bonds of **7** are in contrast to the normal steroidal ketones, which usually show unequal migratory aptitudes.[15]

The 5β isomer **7** exhibited a negative Cotton effect ($a = -28$)[16] as does methyl-2-keto-A-nor-5β-cholanate ($a = -152$).[17] A-nor-5α-cholestan-2-one shows a strong positive Cotton effect ($a = +233$).[17] The increased planarity of the A ring in **7** relative to the A-nor ketones is probably responsible for the greatly reduced amplitude of its Cotton effect.[18,19]

The behavior of the AB-dinorenone **4** toward chemical reduction was of interest, since the factors governing product stereochemistry are still incompletely understood. Treatment of the enone **4** with an excess of lithium in ammonia gave a quantitative yield of the saturated alcohols **12** and **13**. Oxidation of the epimeric alcohols with chromic acid in acetone[20] gave the saturated AB *cis* ketone **7**. No trace of the 5α isomer could be found.[21]

The stereochemistry of reduction of the saturated AB-dinor ketone **7** was briefly studied. Chromatography of the alcohol mixture from lithium–ammonia reduction of **4** gave 80% more polar epimer and 20% less polar epimer. Although exceptions have been noted,[22] it appears reasonable to assume that lithium–ammonia reduction of **7** will yield predominantly the more stable epimer.[23,24] The *exo* epimer is the more stable in 1- and 2-substituted *cis*-bicyclo[3.3.0]octanes.[25] By analogy the 2β configuration is assigned to the major alcohol **13**. The 16β alcohol is also the more stable epimer in the closely related 14β steroids.[26] The 2β configuration of the major alcohol **13** is supported by the fact that it gave a precipitate with digitonin, whereas the minor alcohol **12** did not.[27] The chromatographic mobilities of the two epimers are also in the expected order.[28] Thus, the more exposed 2β epimer (*exo*) is less mobile than the hindered 2α alcohol (*endo*), which cannot interact as strongly with the adsorbent.

The hydride reduction of **7** was the final proof of stereochemistry. Hydride reduction of *cis*-bicyclo[3.3.0]octanones[25a,29] or of 2-keto-A-nor-5β steroids[6a,30] proceeds predominantly by topside attack to give the less stable α alcohols, and it was therefore anticipated that the product distribution from hydride reduction of **7** should be the reverse of that obtained from the lithium–ammonia reduction. Treatment of an ethanolic solution of **7** with sodium borohydride gave a mix-

(13) Formylation could also occur at C-4, but R. O. Clinton, R. Clarke, F. Stonner, A. Manson, K. F. Jennings, and D. Phillips, *J. Org. Chem.*, **27**, 2800 (1962), have shown that condensation usually occurs at C-2 in 5β-3 ketones.

(14) (a) W. S. Johnson, M. Neeman, and S. P. Birkeland, *Tetrahedron Lett.*, 1 (1960); (b) W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Amer. Chem. Soc.*, **84**, 989 (1962); (c) H. O. House, E. J. Grubbs, and W. F. Gannon, *ibid.*, **82**, 4099 (1960).

(15) (a) N. A. Nelson and R. N. Schut, *ibid.*, **81**, 6486 (1959); (b) S. Hara, *Chem. Pharm. Bull.* (Tokyo), **12**, 1531 (1964).

(16) See C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957), for a discussion of ORD nomenclature.

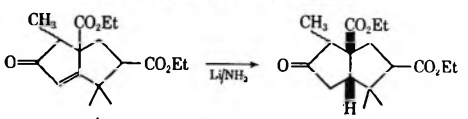
(17) C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6362 (1956).

(18) (a) W. Klyne, *Tetrahedron*, **13**, 29 (1961); (b) P. M. Bourn and W Klyne, *J. Chem. Soc.*, 2044 (1960).

(19) C. Djerassi and J. E. Gurst, *J. Amer. Chem. Soc.*, **86**, 1755 (1964).

(20) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953); (c) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(21) G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.*, **83**, 3114 (1961), have obtained a similar result with a related enone i.



(22) (a) G. Ourisson and A. Rassat, *Tetrahedron Lett.*, 16 (1960); (b) J. W. Huffman, D. M. Alabran and T. W. Bethea, *J. Org. Chem.*, **27**, 3383 (1962).

(23) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).

(24) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(25) (a) R. Granger, P. Nau, and J. Nau, *Bull. Soc. Chim. Fr.*, 1350 (1960), and papers cited therein; (b) A. C. Cope and M. Brown, *J. Amer. Chem. Soc.*, **80**, 2859 (1958).

(26) T. Nambara and J. Fishman, *J. Org. Chem.*, **27**, 2131 (1962).

(27) Although digitonide formation with such a highly modified steroid may be questionable, it should be noted that A-norcholestanols behave normally with regard to digitonide formation.[6a]

(28) A. C. Cope and P. E. Peterson, *J. Amer. Chem. Soc.*, **81**, 1643 (1959).

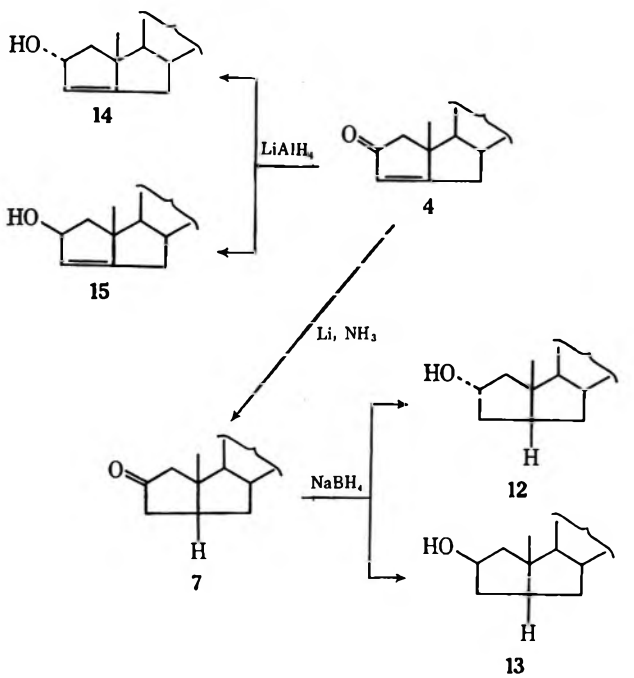
(29) A. C. Cope, M. Brown, and H. Petree, *ibid.*, **80**, 2852 (1958).

(30) K. Yoshida and T. Kubota, *Tetrahedron*, **21**, 759 (1965)

ture of the epimeric alcohols **12** and **13**. Chromatographic separation showed the mixture to consist of approximately 80% less polar α epimer **12** and 20% more polar β epimer **13**, thus confirming our prediction and providing compelling evidence for our assignment of stereochemistry.

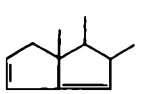
Lithium aluminum hydride reduction of the AB-dinorenone **4** gave a mixture of the epimeric allylic alcohols **14** and **15** (Scheme III) with the more polar

SCHEME III



epimer predominating. The major epimer was obtained in pure form after two recrystallizations from methanol, and was assigned the 2β configuration by analogy with A-norcholestenone[31] and because it formed a digitonide. The increase in α attack in comparison with the saturated ketone **7** is probably a result of the increased planarity of the A ring of **4** and the consequent reduction of hindrance on the α side of the A ring. In addition, the carbonyl group of **4** is more hindered by the 19-methyl group and topside attack is impeded. A similar effect is observed in the related 2-keto steroids.[32]

Treatment of the allylic alcohols **14** and **15** with refluxing ethanolic hydrochloric acid gave $\Delta^{2,5}$-AB-dinorcholestadiene (**16**) in quantitative yield. The



16

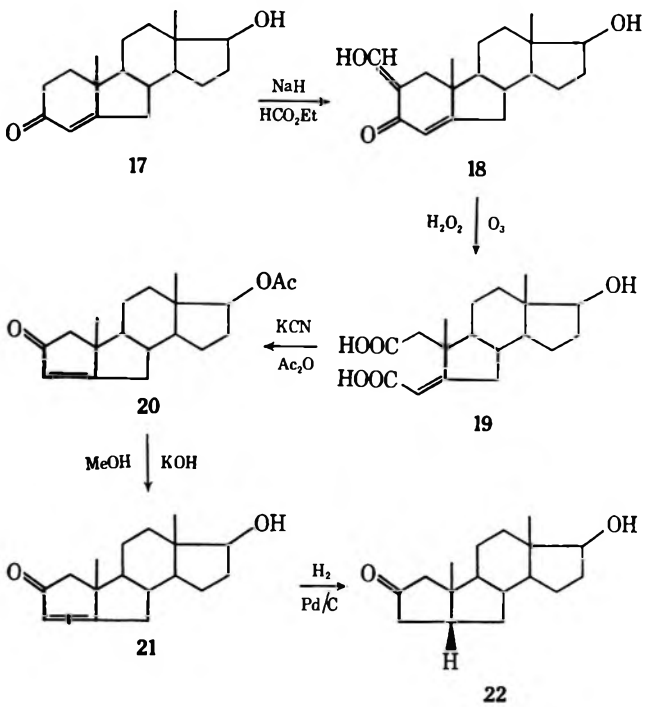
pattern of the vinyl protons in the nmr spectrum was very similar to that of $\Delta^{3,5}$-B-norcholestadiene and conclusively proved the position of the double bonds.

The AB-dinor ketone **7** was subjected to acid-catalyzed bromination to determine the direction of enolization of the 2 ketone. The ketone **7** was completely resistent to bromination. A similar lack of reactivity has been observed with 16-keto steroids[33] and 2-keto-A-nor steroids[6b,12] and is probably a reflection of the increased strain of the enol form.[34]

Although **7** was resistent to bromination it reacted with isopropenyl acetate under forcing conditions[6b] to give a quantitative yield of the Δ^1- and Δ^2-enol acetates in approximately equal amounts. It therefore appears that there is no great preference in the direction of enolization of the AB-dinor ketone **7**.

To determine the biological consequences of contraction of the A and B rings of a steroid hormone, the contraction sequence outlined above was applied to B-nortestosterone (**17**).[35] Treatment of **17** with sodium hydride and ethyl formate gave a 97% yield of the 2-hydroxymethylene derivative **18**, which was selectively ozonized to give the 2,3-seco diacid **19** in 70% yield. Cyclization of **19** in refluxing acetic anhydride containing potassium cyanide gave a 60% yield of AB-dinortestosterone acetate (**20**). Saponification gave AB-dinortestosterone **21**, whose spectral properties confirmed the assigned structure. Hydrogenation of **21** gave a quantitative yield of the 5β ketone **22** (Scheme IV). The ORD curve of **22** was very similar to that of AB-dinor-5β-cholestan-2-one (**7**) and supported the assigned stereochemistry.

SCHEME IV



Compounds **18**, **20**, and **21** were tested[36] for androgenic and antiandrogenic activity by the improved

(31) G. A. Boswell, "Doctoral Dissertation," University of California, Berkeley, Calif., 1959, p 50.

(32) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Amer. Chem. Soc.*, **78**, 3752 (1956).

(33) J. Fajkos and J. Joska, *Coll. Czech. Chem. Comm.*, **25**, 2863 (1960).

(34) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954).

(35) Prepared according to T. Rull and G. Orisson, *Bull. Chim. Soc. Fr.*, 1581 (1958). In the later stages of our work we were kindly supplied with B-nortestosterone benzoate by the Cancer Chemotherapy National Service Center (CCNSC), which prepared the compound by the method of K. Tanabe and Y. Morisawa, *Chem. Pharm. Bull. (Tokyo)*, **11**, 536 (1963), and earlier papers cited therein.

(36) The authors are indebted to Dr. M. L. Hopwood, Dr. R. P. Martin, and G. S. Farnham, who carried out the biological testing at the Endocrine Section of the Department of Chemistry, Colorado State University, Fort Collins, Colo.

chick comb methods of Lerner.[4e,37] None of the compounds showed significant androgenic or antiandrogenic activity at the 95% confidence level. The antiandrogenic activity of the A- and B-nor analogs[4] is therefore not enhanced by further ring contraction. Apparently, the geometry of the AB-dinor analogs has been changed to the point where binding to the receptor can no longer occur. The A- or B-nor analogs are sufficiently similar to the hormone so that receptor binding still takes place, but their altered geometry does not cause the molecular changes leading to an androgenic response.[38] Thus, they are capable of blocking the effect of testosterone without causing an androgenic response themselves.

Experimental Section[39]

2-Hydroxymethylene-B-norcholest-4-en-3-one (2).—A benzene solution (470 ml) of 37.6 g of **1** was treated with ethyl formate (38 ml, 0.47 mol) and sodium hydride (5.64 g, 0.24 mol) according to the procedure of Weisenborn[9] to give 37.2 g (91%) of **2**, mp 100–102°. Three recrystallizations from hexane gave an analytical sample: mp 100–104°; $[\alpha]^{28}D$ −71° (*c* 0.496); λ_{max}^{EtOH} 250 mμ (ε 11,300) and 307 (6800); $\nu_{max}^{CCl_4}$ 2703, 1645, 1567, and 1195 cm.$^{-1}$, nmr (CCl_4) τ −3.87 (1 H, broad, enolic proton), 2.73 (1 H, d, *J* = 8 Hz, hydroxymethylene vinyl), and 4.23 (1 H, t, *J* = 1.5 Hz, C-4 vinyl).

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.07; H, 10.44.

2,3-Seco-B-norcholest-4-ene-2,3-dioic Acid (3).—A solution of 33.2 g (83 mmol) of **2** in 700 ml of 1:1 glacial acetic acid–ethyl acetate was treated with 1 equiv of ozone at −15° and worked up by the method of Weisenborn[9] to give 32.4 g (93%) of **3**, mp 145–160°. Recrystallization from chloroform–hexane gave fine needles that melted with gas evolution at 160–161°: $[\alpha]^{25}D$ + 6.3° (*c* 0.473); λ_{max}^{EtOH} 225 mμ (ε 12,500); $\nu_{max}^{CHCl_3}$ 3484, 1702, 1642, and 1235 cm.$^{-1}$; nmr (CCl_4) τ 2.45 (2 H, broad, OH), 5.20 (1 H, broad, vinyl).

Anal. Calcd for $C_{25}H_{42}O_4$; C, 74.60; H, 10.4. Found: C, 74.82; H, 9.99.

AB-Dinorcholest-3-en-2-one (4).—A solution of 640 mg (1.53 mmol) of **3** and 110 mg (1.69 mmol) of potassium cyanide in 40 ml of acetic anhydride was allowed to reflux under nitrogen for 2 days. The dark brown mixture was evaporated under reduced pressure, and the residue was dissolved in ether and washed with water and 10% potassium hydroxide. The ether solution was evaporated to give 600 mg of a dark brown oil that was chromatographed on 20 g of Woelm neutral activity III alumina. Elution with petroleum ether–benzene (3:1) gave 372 mg (68%) of **4**, mp 50–53°. Four recrystallizations from methanol gave an analytical sample: mp 54–55°; $[\alpha]^{29}D$ −123° (*c* 0.494); λ_{max}^{EtOH} 235 mμ (ε 13,400); $\nu_{max}^{CCl_4}$ 1709 and 1629 cm^{-1}; nmr (CCl_4) τ 4.25 (1 H, t, *J* = 1.5 Hz, vinyl), 7.85 (2 H, s, C-1 methylene), and 7.74–7.98 (2 H, m, C-6 methylene); ORD (c 0.003, cyclohexane) $[\alpha]_{300}$ −1330°, $[\alpha]_{261}^{trough}$ −13,000°, $[\alpha]_{212}^{peak}$ +35,000° (*a* = −1710).

Anal. Calcd for $C_{25}H_{40}O$: C, 84.21; H, 11.31. Found: C, 84.16; H, 11.11.

AB-Dinor-5β-cholestan-2-one (7). A. From Hydrogenation of 4.—A solution of 400 mg (1.12 mmol) of **4** in 20 ml of 95% ethanol was hydrogenated at atmospheric pressure over 100 mg of 5% palladium on charcoal. After 20 min the reaction was complete and 400 mg (99%) of **7** was obtained. Recrystallization from methanol gave an analytical sample: mp 63–64°; $[\alpha]^{30}D$ + 4° (*c* 0.496); λ_{max}^{EtOH} 289 mμ (ε 14); $\nu_{max}^{CCl_4}$ 1742 and 1404 cm^{-1}; nmr (CCl_4) τ 7.79 (4 H, broad, C-1 and C-3 methylenes); ORD (*c* 0.182, methanol) $[\alpha]_{450}$ +8°, $[\alpha]_{312}^{trough}$ −297°, $[\alpha]_{270}^{peak}$ +489° (*a* = −28).

Anal. Calcd for $C_{25}H_{42}O$: C, 83.73; H, 11.81. Found: C, 83.71; H, 11.16.

B. From B-Nor-5β-cholestan-3-one (8).—A suspension of 712 mg (1.92 mmol) of **8**, 100 mg of sodium hydride (4.1 mmol, as a 54% mineral oil dispension), and 0.32 ml (4.0 mmol) of ethyl formate in 50 ml of benzene was allowed to reflux under nitrogen for 24 hr and then worked up as usual[9] to yield 624 mg (82%) of **9** as a yellow oil: $\nu_{max}^{CCl_4}$ 1661, 1590, and 1198 cm^{-1}; nmr (CCl_4) τ 2.84 (1 H, s, hydroxymethylene vinyl) and 7.98 (2 H, m, C-4 methylene).

A solution of 560 mg (1.40 mmol) of crude **9** in 30 ml of glacial acetic acid–ethyl acetate (1:1) was ozonized and worked up as usual[9] to yield 590 mg (99%) of the seco diacid **10**, mp 190–195°. Two recrystallizations from chloroform–hexane gave 420 mg (71%) of **10**: mp 190–201°; $[\alpha]^{28}D$ +26.7° (*c* 0.484); $\nu_{max}^{CCl_4}$ 3400–2500, 1706, and 1278 cm.$^{-1}$; nmr ($CDCl_3$) τ 0.71 (2 H, broad, –COOH) and 7.95 (4 H, m, C-1 and C-4 methylene).

Anal. Calcd. for $C_{26}H_{44}O_4$: C, 74.24; H, 10.54. Found: C, 74.18; H, 10.33.

A solution of 548 mg (1.31 mmol) of **10** and 340 mg of potassium cyanide (5.24 mmol) in 25 ml of acetic anhydride was allowed to reflux under a nitrogen atmosphere for 24 hr and worked up as described for **4** to yield 150 mg (33%) of **7**, mp 45–55°. Two recrystallizations from methanol gave material melting at 61–63° that was identical in all respects with that obtained from the hydrogenation of **4**.

Diazomethane Homologation of AB-Dinor-5β-cholestan-2-one (7).—A solution of 50 mg (0.14 mmol) of **7** (from hydrogenation of **4**) and 0.3 ml of catalyst solution[14b] (1 ml of boron trifluoride etherate in 25 ml of 3:1 methylene chloride–ether) in 10 ml of anhydrous methylene chloride was treated with 0.18 mmol of diazomethane for 1 hr at 0° and then worked up[14b] to give 77 mg of a clear oil: $\nu_{max}^{CCl_4}$ 1742 and 1718 cm^{-1}. Chromatography on 10 g of Woelm activity III neutral alumina gave 7 mg (13%) of homologated material upon elution with 1:1 petroleum ether–benzene. Gas chromatography on a 1% polyester column showed that the product consisted of approximately equal amounts of the 2- and 3-keto-B-nor-5β-cholestanes **11** and **8**.

Lithium–Ammonia Reduction of AB-Dinorcholest-3-en-2-one (4).—A solution of 103 mg (0.29 mmol) of **4** in 25 ml of liquid ammonia and 10 ml of ether was reduced with 200 mg of lithium to give 110 mg of a mixture of the 2α and 2β alcohols **12** and **13**. Chromatography on alumina showed the mixture to consist of approximately 80% 2β alcohol **13** which was recrystallized from methanol: mp 120–123°; $[\alpha]^{29}D$ +25° (*c* 0.489). The 2β alcohol (7.3 mg in 11 ml of 95% ethanol) gave a precipitate with digitonin (31.8 mg in 1.6 ml of 70% ethanol).

Anal. Calcd for $C_{25}H_{44}O$: C, 83.27; H, 12.30. Found: C, 83.40; H, 12.05.

Oxidation[20] of 17 mg of a 1:1 mixture of the alcohols **12** and **13** gave 15 mg (88%) of **7** that was identical with the material obtained from hydrogenation of **4**.

Sodium Borohydride Reduction of AB-Dinor-5β-cholestan-2-one (7).—A solution of 100 mg (0.28 mmol) of **7** in 50 ml of 95% ethanol was treated with 100 mg (2.63 mmol) of sodium borohydride to give 100 mg of a mixture of the 2α and 2β alcohols **12** and **13**, which was chromatographed on 20 g of alumina (activity III). Elution with benzene gave 66 mg (66%) of the 2α alcohol **12**: mp 89–91°; $[\alpha]^{25}D$ +15° (*c* 0.466). An insoluble digitonide was not formed.

Anal. Calcd for $C_{25}H_{44}O$: C, 83.27; H, 12.30. Found: C, 82.99; H, 12.18.

Continued elution with benzene gave 21 mg (21%) of the 2β alcohol **13**: mp 117–120°; $[\alpha]^{30}D$ +25° (*c* 0.489).

Lithium Aluminum Hydride Reduction of AB-Dinorcholest-3-en-2-one (4).—To a refluxing suspension of 38 mg (1.0 mmol) of lithium aluminum hydride in 25 ml of anhydrous tetrahydrofuran was added a solution of 250 mg (0.70 mmol) of **4** in 25 ml of anhydrous tetrahydrofuran over a period of 30 min. The mixture was allowed to reflux under N_2 for 5 hr and was then worked up with saturated ammonium chloride to give 242 mg of the 2α- and 2β-allylic alcohols **14** and **15**. Two recrystallizations of the crude reaction mixture from methanol gave the major epimer **15** in pure form: mp 105–107°; $[\alpha]^{26}D$ −22.4° (*c* 0.490).

Anal. Calcd for $C_{25}H_{42}O$: C, 83.73; H, 11.81. Found: C, 83.87; H, 11.70.

AB-Dinorcholesta-2,5-diene (16).—A solution of 70 mg (0.195 mmol) of a 1:1 mixture of **14** and **15** and 0.2 ml of concentrated

(37) L. J. Lerner and A. Bianchi, *Acta Endocrinol.*, **44**, 389 (1963).

(38) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

(39) Melting points were determined with a Mel-Temp apparatus in evacuated, sealed capillaries and are uncorrected. Optical rotations were taken in chloroform. Infrared spectra were obtained with a Perkin-Elmer Model 137-B or Model 237 spectrometer. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 or a Cary Model 14 spectrometer. Nmr spectra were obtained with a Varian Associates Model A-60 spectrometer using tetramethylsilane as internal standard. ORD curves were recorded with a Cary Model 60 spectropolarimeter. Microanalyses were performed by the Microchemical Laboratory, College of Chemistry, University of California.

HCl in 20 ml of absolute ethanol was heated under reflux for 5 hr to give 65 mg (98%) of a pale yellow oil. Two recrystallizations from methanol gave 55 mg (80%) of **16**: mp 70–71°; $[\alpha]^{27}D$ −136° (*c* 0.472); $\nu_{max}^{CS_2}$ 837, 813, 734, and 698 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 238 mμ (ε 9410), 245 (9860), and 253 (6570); nmr (CCl_4) τ 3.92 (1 H, doublet of triplets, $J_{2,3}$ = 10 Hz, $J_{1,3}$ = 2 Hz, C-3 vinyl), 4.38 (1 H, d, $J_{2,3}$ = 10 Hz, C-2 vinyl), 4.66 (1 H, s, C-7 vinyl), and 7.93 (3 H, m, allylic).

Anal. Calcd for $C_{25}H_{40}$: C, 88.16; H, 11.84. Found: C, 87.87; H, 11.60.

Enol Acetylation of AB-Dinor-5β-cholestan-2-one (7).—A solution of 2.00 g (5.58 mmol) of **7** and 0.40 g of *p*-toluenesulfonic acid in 200 ml of redistilled isopropenyl acetate was allowed to reflux for 3 days under forcing conditions.[6b] Chromatography of the crude product on silica gel gave 2.3 g of an oil that crystallized from methanol to give 2.10 g (97%) of an approximately 1:1 mixture of the Δ^1- and Δ^2-enol acetates of **7**: mp 36–37°; $\nu_{max}^{CCl_4}$ 1766, 1665, 1645, and 1215 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 193 mμ (ε 9680); nmr (CCl_4) τ 4.72 (1 H, m, vinyls) and 7.99 (3 H, s, acetyl).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.83; H, 11.30.

17β-Hydroxy-2-hydroxymethylene-B-norandrost-4-en-3-one (18).—A suspension of 1.79 g (6.53 mmols) of B-nortestosterone (**17**), 1.88 ml (23.5 mmol) of ethyl formate, and 0.56 g (23.6 mmol) of sodium hydride in 38 ml of benzene was stirred under N_2 for 3 days at room temperature and worked up as usual[9] to give 1.95 g (99%) of **18**. Recrystallization from methylene chloride–petroleum ether gave an analytical sample: mp 214–216°; $[\alpha]^{25}D$ −73° (*c* 0.430); $\nu_{max}^{CHCl_3}$ 3450, 1640, and 1562 cm^{-1}; λ_{max}^{EtOH} 250 mμ (ε 11,300) and 307 (6810).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.66. Found: C, 75.37; H, 8.66.

17β-Hydroxy-2,3-seco-B-norandrost-4-ene-2,3-dioic Acid (19).—A solution of 1.00 g (3.31 mmol) of **18** in 30 ml of 1:1 glacial acetic acid–ethyl acetate was treated with 3.31 mmol of ozone at −15° to give 0.74 g (69%) of crystalline seco diacid **19**, mp 212–214°. Recrystallization from aqueous methanol gave an analytical sample: mp 230–232°; $[\alpha]^{25}D$ −46° (*c* 0.450); ν_{max}^{KBr} 3330, 2597, 1712, and 1645 cm^{-1}; λ_{max}^{EtOH} 223 mμ (ε 12,600); nmr (CH_3OD) τ 5.30 (1 H, m, vinyl).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.86; H, 8.11.

17β-Hydroxy-AB-dinorandrost-3-en-2-one Acetate (20).—A solution of 4.75 g (14.75 mmol) of **19** and 3.82 g (59 mmol) of KCN in 250 ml of acetic anhydride was allowed to reflux under argon for 2 days and then worked up as described for **4**. Chromatography of the crude product on alumina gave 3.03 g (68%) of an oil, which was crystallized from methylene chloride–petroleum ether to give 2.64 g (60%) of crystalline **20**: mp 109–112°; $[\alpha]^{26}D$ −155° (c 0.491); ν_{max}^{CCl} 1742, 1712, and 1633 cm^{-1}; λ_{max}^{EtOH} 235 mμ (ε 13,500); nmr ($CDCl_3$) τ 4.25 (1 H, t, *J* = 1.5 Hz, vinyl), 5.40 (1 H, t, *J* = 7 Hz, 17α H), 7.97 (3 H, s, acetyl), 8.94 (3 H, s, C-19), and 9.13 (3 H, s, C-18).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 75.46; H, 8.67. Found: C, 75.53; H, 8.45.

17β-Hydroxy-AB-dinorandrost-3-en-2-one (21).—A solution of 2.64 g (8.75 mmol) of **20** and 5 g of KOH in 125 ml of 95% methanol was allowed to reflux for 1 hr under nitrogen to give 1.9 g of crude **21** that was chromatographed on alumina to yield 1.70 g of crystalline **21**, mp 114–116°. Recrystallization from methylene chloride–petroleum ether gave an analytical sample: mp 116–117°; $[\alpha]^{25}D$ −150° (*c* 0.479); $\nu_{max}^{CCl_4}$ 3610, 3448, 1709, and 1626 cm^{-1}; λ_{max}^{EtOH} 235 mμ (ε 13,500); nmr ($CDCl_3$) τ 4.24 (1 H, t, *J* = 1.5 Hz, vinyl), 6.32 (1 H, t, *J* = 7.5 Hz, 17α H), and 7.78 (2 H, s, C-1 methylene); ORD (*c* 0.0024, ethanol) $[\alpha]_{400}$ −553°, $[\alpha]_{250}^{trough}$ −18,700°, $[\alpha]_{215}^{peak}$ +44,200° (*a* = −1636).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.40; H, 9.29. Found: C, 78.13; H, 9.27.

17β-Hydroxy-AB-dinor-5β-androtan-2-one (22).—A solution of 515 mg (1.98 mmol) of **21** in 50 ml of 95% ethanol was hydrogenated at atmospheric pressure over 50 mg of 5% palladium on charcoal to give 514 mg (99%) of **22**, mp 128–130°. Two recrystallizations from chloroform gave an analytical sample: mp 131–133°; $[\alpha]^{29}D$ −10° (*c* 0.460); $\nu_{max}^{CCl_4}$ 1739 cm^{-1}; nmr ($CDCl_3$) τ 8.93 (3 H, s, C-19) and 9.25 (3 H, s, C-18); ORD (c 0.085, methanol) $[\alpha]_{400}$ −24°, $[\alpha]_{311}^{trough}$ −530°, $[\alpha]_{272}^{peak}$ + 647° (*a* = −30.9).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.90. Found: C, 77.57; H, 9.82.

Registry No.—**2**, 19955-03-4; **3**, 19933-87-0; **4**, 19933-77-8; **7**, 19933-78-9; **7** (Δ^1-enol acetate), 19933-79-0; **7** (Δ^2-enol acetate), 19933-80-3; **10**, 19933-89-2; **12**, 19955-04-5; **13**, 19933-81-4; **15**, 19955-05-6; **16**, 19933-82-5; **18**, 19933-83-6; **19**, 19933-88-1; **20**, 19933-86-9; **21**, 19933-84-7; **22**, 19933-85-8.

Photoisomerization of Acyclic Conjugated Cyclopropyl Carbonyl Compounds[1]

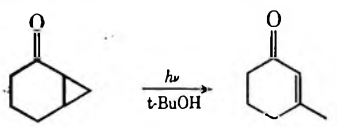
WILLIAM G. DAUBEN AND GARY W. SHAFFER[2]

University of California, Berkeley, California 94720, and Givaudan Corporation, Clifton, New Jersey 07014

Received December 30, 1968

The photochemistry of the acyclic vinylcyclopropane carbonyl chromophore has been studied. Using Corex-filtered light, dihydrofurans (**4**–**6**), δ,ε-unsaturated acids (**7** and **8**), and epoxycyclobutanes (**9** and **10**) were found. The mechanism for the formation of these materials are discussed, and all reactions involve conjugative opening of the cyclopropane ring (eq 6 and 7). The formation of a ketene from an acyclic aldehyde is a new process and it has been shown to proceed intramolecularly (eq 8).

The photoisomerization of the cyclopropyl carbonyl chromophore, when contained in a bicyclic system, has been shown generally to bring about the cleavage of the better overlapped bond of the cyclopropyl ring. For example, bicyclo[4.1.0]heptan-2-one upon photolysis in *t*-butyl alcohol yields 3-methylcyclohexenone (eq 1).[3]



(1)

When this chromophore is not geometrically constrained into a fused-ring system, isomerization to an α,β-unsaturated enone still occurs if the cyclopropyl ring is unsubstituted (eq 2);[4] however, when the cyclopropyl ring is substituted with an alkyl group *cis* to the carbonyl group, only a Norrish type II reaction is observed (eq 3).[5]

The related ene-cyclopropane-one chromophore when contained in a bicyclo[3.1.0]hexane ring system, the so-

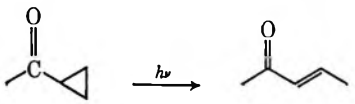
(1) This work was supported in part by PHS Grant No. 00709, National Institutes of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) National Institutes of Health Predoctoral Fellow, 1965–1967.

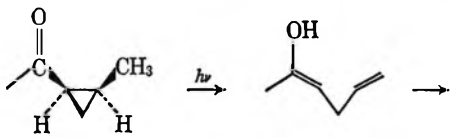
(3) W. G. Dauben and G. W. Shaffer, *Tetrahedron Lett.*, 4415 (1967).

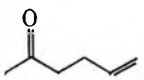
(4) J. N. Pitts, Jr., and I. Norman, *J. Amer. Chem. Soc.*, **76**, 4815 (1954); L. D. Hess, J. L. Jacobsen, K. Schaffner, and J. N. Pitts, Jr., *ibid.*, **89**, 3684 (1967).

(5) W. G. Dauben, L. Schutte, and R. E. Wolf, *J. Org. Chem.*, **34**, 1849 (1969).



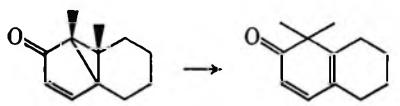
(2)



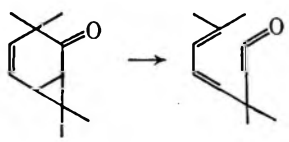


(3)

called lumiproduct of cross-conjugated cyclohexadienones, also undergoes photoisomerization involving cleavage of the cyclopropane ring (eq 4).[6] However, when this chromophore is part of a bicyclo[4.1.0]heptane system, the photoreaction yields an acyclic ketene (eq 5).[7] This vinylcyclopropane carbonyl



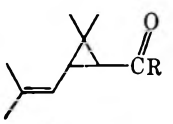
(4)



(5)

system has now been studied in an acyclic system in order to evaluate the various steric and electronic factors involved in the photoisomerization of this chromophore.

The materials chosen for this study were 2,2-dimethyl - 3 - [1′ - (2 - methylpropenyl)]cyclopropylcarboxaldehyde (**1**), 2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde-d_1 (**2**), and 1-acetyl-2,2 - dimethyl - 3 - [1′ - (2 - methylpropenyl)]cyclopropane (**3**). The syntheses of these compounds from ethyl chrysanthemumate is described in the Experimental Section. As prepared, each material was a mix-

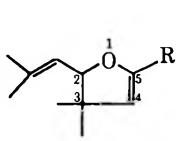


1, R = H
2, R = D
3, R = CH_3

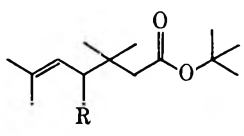
ture of the *cis* and *trans* isomer and this mixture could be resolved on a Carbowax vpc column. The assignment of the stereochemical configuration was made on the basis of the nmr spectra and the behavior of the mixture on a vpc column which had been impregnated with potassium hydroxide. It has been shown[8] for chrysanthemumic acid and its *t*-butyl ester that the olefinic proton nmr absorption occurs at higher field for the *trans* isomer than for the *cis* isomer. Injection of a *cis–trans* mixture of **1** or **2** on a basic Carbowax column, followed by collection and reinjection on a neutral Carbowax column, shows an increase in the percentage of that isomer which is eluted first. The *trans* isomer is thermodynamically more stable than the *cis* isomer and Julia has shown[9] that *cis* chrysanthemumic esters, when treated with base and saponified, yielded mainly the *trans* acid. On this basis, the isomer whose vinylic nmr absorption is at the higher field and which is eluted first from a Carbowax vpc column is assigned the *trans* configuration.

The irradiations of **1**–**3** were carried out in dilute *t*-butyl alcohol solutions with Corex-filtered (>255 mμ) light. Photointerconversion of the *cis–trans* isomers of **1**–**3**, an expected reaction of conjugated cyclopropyl carbonyl compounds, was observed in each case. Solutions of either **1** or **2**, consisting of mainly the *trans* isomer before irradiation, showed a rapid decrease of this isomer and an increase of the *cis* isomer after light exposure for 0.5–1.0 hr. In the case of **3**, the percentage of the *cis* isomer never increased over that present prior to irradiation; however, its rate of disappearance was much slower than for the *trans* isomer.

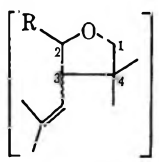
Both aldehydes **1** and **2** yielded three photoproducts, which were isolated by preparative vpc after solvent removal. The major products from each irradiation, eluted from vpc shortly after the solvent *t*-butyl alcohol, were obtained in 61 and 51%, respectively, and were



4, R = H
5, R = D
6, R = CH_3



7, R = D
8, R = H



9, R = H
10, R = D

identified as 2-[1′-(2-methylpropenyl)]-3,3-dimethyl-Δ^4-dihydrofuran (**4**) and 2-[1′-(2-methylpropenyl)]-3,3-dimethyl-5-deuterio-Δ^4-dihydrofuran (**5**), respectively. Mass spectra indicated the compounds were isomeric with **1** and **2** and ir spectra showed the absence of carbonyl or hydroxyl functions. Identification was made on the basis of the nmr spectra, which showed the very characteristic vinylic proton absorptions for a dihydrofuran.[10] The spectrum of **4** has a doublet at τ 3.87 (J = 2.5 Hz) for the proton at C-5 and a doublet at τ 5.26 (J = 2.5 Hz) for the proton at C-4. The spectrum of **5** is identical with that of **4** except that the doublet at τ 3.87 is no longer present and the doublet at τ 5.26 has changed to a singlet at τ 5.26, thus proving that the aldehydic proton becomes the C-5 proton of the dihydrofuran photoproduct.

The remainder of the nmr spectrum of **4** showed the expected absorptions (see Experimental Section) for four methyl groups, two of which reside on a double bond, and for one additional vinylic proton. The final proton appeared as a sharp doublet at τ 5.43 (J = 9 Hz). This low-field position indicates that the hydrogen must be both allylic and geminal to the oxygen atom, therefore the methylpropenyl side chain must be located at C-2.

(6) P. J. Kropp, "Organic Photochemistry," Vol. 1, O. L. Chapman, Ed., M. Dekker, Inc., New York, N. Y., 1967, pp 1–86.
(7) A. J. Bellamy and G. H. Whitman, *J. Chem. Soc.*, 4035 (1964).
(8) T. Matsumoto, A. Nagai, and Y. Takahashi, *Bull. Chem. Soc. Jap.*, **36**, 481 (1963).
(9) M. Julia, S. Julia, B. Bemont, and G. Tchernoff, *C. R. Acad. Sci., Paris*, **248**, 242 (1959); *Chem. Abstr.*, **53**, 17922*g* (1959).
(10) L. M. Jackman, "Applications of NMR Spectroscopy in Organic Chemistry," The Macmillan Co., New York, N. Y., 1964, p 62.

Similarly, 2-[1′-(2-methylpropenyl)]-3,3,5-trimethyl-Δ^4-dihydrofuran (**6**) was the major photoproduct (52%) from the irradiation of **3**. The vinylic proton on the dihydrofuran ring has nmr absorption at τ 5.45 (broadened singlet), thus showing that the methyl group is attached at C-5.

Dihydrofuran **4**, when isolated and irradiated without a filter, yielded small amounts of two products whose vpc retention times were identical with those of *cis* and *trans* **1**. This photoisomerization of a dihydrofuran to a vinylcyclopropylcarboxaldehyde has already been observed.[11]

The second photoproduct from **1** and **2**, found in 14 and 10% yield, respectively, was identified as *t*-butyl 3,3,6-trimethyl-Δ^5-heptenoate (**7**) and *t*-butyl 3,3,6-trimethyl-4-deuterio-Δ^5-heptenoate (**8**), respectively. The mass spectrum of **7** has the last peak at 170, which is consistent with the facile loss of isobutylene from *t*-butyl esters. An ester was also indicated from infrared absorptions at 1727, 1170, and 1140 cm^{-1}. Samples of **7**, vpc collected, were always contaminated with *cis* **1** and the nmr spectrum was run with impure material. This caused no difficulties with the interpretation except for the vinylic absorption of ester **7**. The expected triplet for the vinylic proton of **7** actually appeared in the 60-Mc spectrum as a broad quartet at τ 4.49–5.01. However, a 100-Mc spectrum resolved this quartet into a doublet at τ 4.64 for *cis* **1** and the triplet (J = 7.5 Hz) at τ 4.79 for ester **7**. The remainder of the spectrum (see Experimental Section) was consistent with **7** and peaks for *cis* **1** could be easily subtracted.

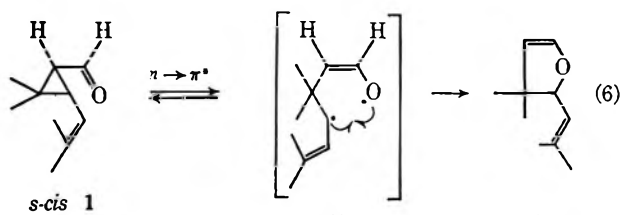
A mass spectrum of the ester isolated from the irradiation of **2** has the molecular ion at 171 with no detectable peak at 170; therefore, the one deuterium of **2** has quantitatively retained during formation of the ester. A 100-Mc nmr spectrum of **8** is essentially identical with that of **7** except that the absorption for the vinylic proton has changed from a triplet at τ 4.79 (J = 7.5 Hz) to a broad doublet at τ 4.82 (J = 7.5 Hz), thus proving that the deuterium is located at C-4 of the ester.

The third photoproduct from **1** and **2**, found in 11 and 10% yield, respectively, has been tentatively identified as *cis*- and *trans*-1,2-epoxy-3-[1′-(2-methylpropenyl)]-4,4-dimethylcyclobutane (**9**) and *cis*- and *trans*-1,2-epoxy-2-deuterio-3-[1′-(2-methylpropenyl)]-4,4-dimethylcyclobutane (**10**), respectively.

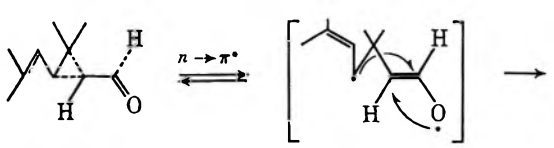
The nmr spectrom of **9** shows absorption for one vinylic proton (broad peak), two protons geminal to the oxygen atom, one allylic proton (two broad doublets), two vinylic methyl groups, and four other methyl groups. The assignment of a *cis–trans* mixture was made on the basis that the allylic proton absorption appears as two nonequivalent doublets and the methyl absorption as four nonequivalent signlets; both assignments were confirmed by the 100-Mc spectrum.

The spectrum indicates that the methylpropenyl side chain is still intact, which, in addition to the two methyl groups situated at fully substituted centers, accounts for six of the original ten carbon atoms. Therefore, the remaining four carbon atoms and one oxygen atom must compose two rings in order to account for the three unsaturation sites of **1**, since there is no indication of a second double bond and the mass spectrum shows the compound to be isomeric with **1**. There are not many possibilities for such a ring system and the choice, represented by **9** and **10**, was based mainly on the fact that this type of ether could logically arise from **1** or **2** in a manner similar to the formation of **4–6**. Ether **10** has retained the deuterium atom at a carbon geminal to the oxygen atom but the deuterium could not be shown conclusively to reside at C-2. Therefore, structures **9** and **10** must remain equivocal at this time. Products analogous to **7** or **9** were not found in the irradiation of the ketone **3**.

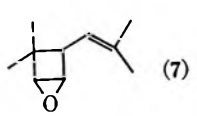
Turning now to a brief consideration of the mechanistic aspects of these photochemical transformations, it is important to appreciate that initial excitation is restricted by the Corex filter to the carbonyl n → π^* band; therefore, reaction is expected to occur through rupture of one of the cyclopropyl bonds which is conjugated with the electronically excited carbonyl group. The dihydrofuran photoproducts, which are photoisomerized to starting ketone using unfiltered light, are viewed as simply a cyclization of the diradical formed when carbonyl n → π^* excitation induces cleavage of that cyclopropyl arm which is cross conjugated with the double bond and the carbonyl group (eq 6). The reason the other conjugated cyclopropane bond does not open is probably because intermediate **11** with a secondary allylic radical is the more stable. It is possible that **1–3** concertedly cyclize to **4–6**, however, the *cis–trans* interconversion of **1–3** implies that **11** is first formed and then recyclizes either to starting material or to product.



s-cis **1** **11** **4** (6)



s-trans **1**



(7)

9

The photoequilibrium *cis–trans* ratio of **1–3** could not be determined owing to the rapid formation of **4–6**, but apparently this equilibrium lies in the direction of the *cis* isomer. There is no obvious reason why the thermodynamically less stable isomer should be photochemically more stable; the uv spectra of the two isomers are very similar.

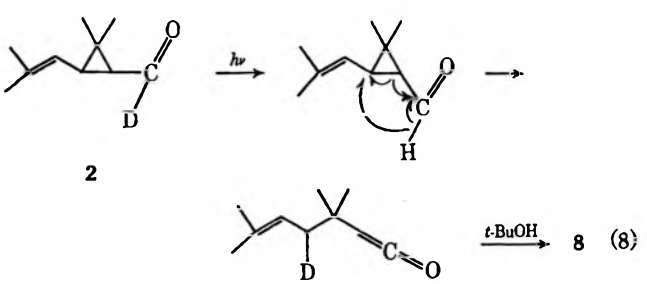
Cyclopropanes **1–3** can exist in either *s-cis* or *s-trans* configurations and once excitation and bond cleavage occurs this configuration is frozen because of the double-bond character between the carbonyl group and the

(11) J. Wiemann, N. Thoai, and F. Weisbuch, *Bull. Soc. Chim. Fr.*, 575 (1966); P. Scribe, M. R. Monot, and J. Wiemann, *Tetrahedron Lett.*, 5157 (1967).

cyclopropyl ring. Dihydrofuran formation is most certainly restricted to the *s-cis* isomer (eq 6), which suggests that *s-trans* **1** might cyclize to epoxycyclobutane **9** (eq 7). This would also explain the absence of a product analogous to **9** (R = CH_3) for methyl ketone **3** because the acetyl methyl group introduces steric hindrance to *s-trans* **3** whereas *s-cis* **3** is relatively unaffected.[12]

Formation of dihydrofurans **4–6** have very little literature precedent, but can be thought of as the oxygen-containing analog to the known rearrangement, both thermally[13] and photochemically,[14] of conjugated vinylcyclopropanes to cyclopentenes.

The formation of esters **7** and **8** is a new type of rearrangement for cyclopropyl carbonyl compounds. Mechanistically, the ester can arise by the transfer of the aldehydic proton to the β position of the cyclopropyl ring with formation of a ketene which then would be expected to yield an ester by reaction with *t*-butyl alcohol (eq 8). There is no experimental evidence for



(8)

the formation of the proposed ketene; however, it already has been demonstrated[15] that the photochemical formation of acids and esters from carbonyl compounds occurs through reaction of a hydroxyl solvent with a ketene.

The hydrogen transfer step of eq 8, which is entirely intramolecular, could occur through a solvent-caged diradical as depicted or could be completely concerted. In either case, some electronic interaction between the cyclopropyl ring and the excited carbonyl group must occur prior to hydrogen migration because the migration specifically occurs to only one of the two β positions of the cyclopropyl ring.

The absence of a product analogous to **7** (R = CH_3) from ketone **3** is consistent with the fact that alkyl radical migrations are far less common than hydrogen atom migrations.

The reactions of vinylcyclopropyl carbonyl compounds **1–3** are probably quite general for this chromophore provided that the carbonyl group and the cyclopropyl ring are not part of a fused skeleton such that cyclization would be prevented by the geometry of the system.

Rearrangements like those observed in eq 2 and 3 were not observed for compounds **1–3** which indicates that the electronic effect of the double bond must be the influential factor leading to the observed photoproducts.

An interesting sidelight to these photorearrangements is the fact that the mass spectra of dihydrofurans **4–6** are extremely similar to the spectra of the respective cyclopropanes **1–3**. This implies that these cyclopropane–dihydrofuran interconversions might also be induced by electron impact as well as photon absorption.

Experimental Section

Irradiations, except where noted, were conducted using a Hanovia 450-W mercury arc lamp (679A-36) inserted into a water-cooled, quartz immersion probe. The filter employed was Corex (9700) which was a glass sleeve insertable between the lamp and the probe. Solutions were stirred and degassed with argon for a minimum of 1 hr preceding irradiation. Argon was continuously bubbled through the solution during irradiation. Irradiation *t*-butyl alcohol was prepared by refluxing and distilling commercial *t*-butyl alcohol from sodium.

Irradiations were monitored by vapor phase chromatography (vpc) on a Carbowax 20M column using a hydrogen flame detector. The percentage of nonmonomeric material formed in the irradiation was arrived at indirectly through integration of the starting material vpc trace before irradiation and the photoproducts plus starting material vpc trace after irradiation. The per cent decrease in the total peak areas after irradiation, using a constant volume injection, was used as an approximate percentage of nonmonomeric material and is probably accurate to 5–10%.

2,2-Dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde (1)—To a stirred solution of 5.50 g (0.0357 mol) of 2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarbinol, prepared by lithium aluminum hydride reduction of ethyl chrysanthemumate (Benzol Products), in 60 ml of reagent-grade acetone, cooled in an ice bath, was added, rapidly but dropwise, 8.0 ml (0.032 mol) of Jones reagent.[16] After addition, the mixture was stirred for 1 min and then diluted with 300 ml of water and 100 ml of ether. The layers were separated and the aqueous phase was extracted with two 100-ml portions of ether. The combined ethereal extracts were washed with two 25-ml portions of 5% sodium carbonate solution, dried, and concentrated.

Distillation of the colorless oil (5.04 g) yielded pure 2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde (1): 1.678 g (31% yield; 74% *trans* 1 and 25% *cis* 1); bp 58–59° (3 mm); mass spectrum, trace peak at 152, peak at 137 (m − 15), very large peak at 123 (m − 29); ν_{max} 2732 (m), 1704–1706 (s), 978 (m), 850 cm^{-1} (m) [spectra of *cis* and *trans* 1 were very similar but had definite differences in the fingerprint region; *trans* had ν_{max} 1110 cm^{-1} (s) and *cis* had ν_{max} 1136 (m), 1115 (m), 1052 cm^{-1} (m)]; $\lambda_{max}^{95\%\ EtOH}$, a sample consisting of mainly *trans* 1 had 198 mμ (ϵ 14,000), 229 shoulder (4450), 283 shoulder (423), a sample consisting of mainly *cis* 1 had 198 mμ (ϵ 14,400), 231 shoulder (2720), $\epsilon_{283\ m\mu}$ 335; nmr (τ, ppm, CCl_4) 0.77 (*trans*) and 0.85 (*cis*) (0.9 H, two doublets which appeared as three peaks, J_t = 5 Hz, J_c = 6 Hz, aldehydic H), 4.64 (*cis*) and 5.11 (*trans*) (1.0 H, two broad doublets, J_c = 7 Hz, J_t = 7.5 Hz, vinylic H), 7.62–8.54 (7.4 H, multiplet with a strong broad singlet at 8.31, vinylic methyl and cyclopropyl H), 8.55–9.04 (6.7 H, multiplet with strong singlets at 8.68 (*cis*), 8.72 (*trans*), 8.79 (*cis*), and 8.84 (*trans*) (methyl and cyclopropyl H). A 100-Mc nmr resolved the three-peak aldehydic H absorption into two doublets, confirmed the vinylic H doublets, and confirmed the four methyl singlets.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.71; H, 10.77.

cis and *trans* 1 could be resolved by vpc on a 20% Carbowax 20M column (*trans* retention time relative to *cis* equaled 0.90). The isomer assignment was made by base isomerization of 1. A mixture of 46% *trans* 1 and 54% *cis* 1 was eluted from a 20% Carbowax 20M–10% KOH column (5 ft × 0.25 in.) as a single symmetrical peak. This peak was collected and its ir spectrum was identical with that of a sample consisting of mainly the *trans* isomer. This peak, reinjected on a plain Carbowax 20M column (5 ft × 0.25 in.), was again resolved into two peaks in the ratio of 74% *trans* and 23% *cis*. Repetition of this process isomerized an 80% *trans*–20% *cis* mixture to 84% *trans* and 13% *cis*. Molecular models indicate that *trans* is the thermodynamically favored isomer; therefore, the isomer which increased when 1 was injected on the basic column was assigned the *trans* configuration.

(12) J. L. Pierre and P. Arnaud, *Bull. Soc. Chim. Fr.*, 2299 (1967).

(13) M. C. Flowers and H. M. Frey, *J. Chem. Soc.*, 3547 (1961); C. S. Elliott and H. M. Frey, *ibid.*, 345 (1965).

(14) P. J. Kropp, *J. Amer. Chem. Soc.*, **89**, 1126 (1967).

(15) G. Quinkert, E. Blanke, and F. Hamburg, *Chem. Ber.*, **97**, 1799 (1964).

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

2,2-Dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde-d_1 (2).—The synthesis was carried out as described above using 6.54 g (0.0419 mol) of 2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarbinol-d_2, prepared by lithium aluminum deuteride reduction of ethyl chrysanthemumate, and 10.0 ml (0.040 mol) of Jones reagent. Work-up and distillation of the colorless oil (4.87 g) yielded 2.11 g of recovered alcohol (32%), bp 70–72° (2.5–3.0 mm), and 2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde-d_1 (**2**): 0.710 g (12% yield; 67% *trans* **2**, 29% *cis* **2**, and 4% of alcohol starting material and another impurity); bp 54–55° (2.5–3.0 mm); mass spectrum, trace peak at 153, peak at 138 (m − 15), very large peak at 123 (m − 30); ν_{max} 2075 (m), 1686 (s), 1374 (m), 1111 (s), 942 (w), 847 cm^{-1} (w); nmr (τ, ppm, CCl_4), the spectrum was essentially identical with that of a *cis–trans* mixture of undeuterated 2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde (**1**) except that the aldehydic proton absorption at 0.77 and 0.85 had completely disappeared.

1-Acetyl-2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropane (3).—From 50.0 g (0.250 mol) of ethyl chrysanthemumate, according to the procedure of Corey,[17] there was obtained 1-acetyl-2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropane (**3**): 18.1 g (44% over-all yield, *cis* and *trans* mixture with *trans* predominating); mass spectrum, last peak at 166, peak at 151 and base peak at 123; ν_{max} 1701 (s), 1376 (m), 1193 (m), 1172 (m), 1112 (m), 952 (m), 851 cm^{-1} (m); uv$^{abs\ EtOH}$ sample consisted of mainly *trans* **3**, $\epsilon_{280\ m\mu}$ 205, $\epsilon_{233\ m\mu}$ 5580 (shoulder), $\epsilon_{210\ m\mu}$ 9850; nmr (τ, ppm, $CDCl_3$) 4.56 (*cis*, broad absorption) and 5.06 (*trans*, doublet, J = 7.5 Hz) (1.0 H, vinylic H), 7.64–8.10 (4.7 H, multiplet with the acetyl methyl absorptions at 7.78 (*trans*, singlet) and 7.80 (*cis*, singlet)), 8.31 (6.6 H, broad singlet, vinylic methyl H), 8.79 (*cis*) and 8.83 (*trans*) (5.7 H, two singlets, methyl H).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.28; H, 10.94.

Irradiation of 2,2-Dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde (1).—A solution of 398 mg of 2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde (80% *trans*–20% *cis*) in 125 ml of *t*-butyl alcohol (0.021 *M*) was irradiated 6.25 hr using Corex-filtered light. The vpc monitor showed the formation of three photoproducts with the following yields at the end of the irradiation: 61% product A (retention time relative to *cis* **1** equaled 0.23), 11% product B (retention time relative to *cis* **1** equaled 0.37), 14% product C (retention time relative to *cis* **1** equaled 0.87, this product was unresolved from *trans* **1**), 6% *cis* **1**, and 8% several minor products and nonmonomeric material. Also, the monitor showed that *trans* **1** was photoisomerized to *cis* **1**; before irradiation there was 80% *trans* and 20% *cis*, after 0.5 hr there was 46% *trans* and 44% *cis*, and after 1.25 hr there was 18% *trans* and 43% *cis*.

Solvent was removed and the three photoproducts were isolated by vpc of the colorless oil (382 mg) on a 20% Carbowax 20M column (5 ft × 0.25 in.). The 61% photoproduct (A) was identified as 2-[1′-(2-methylpropenyl)]-3,3-dimethyl-Δ^1-dihydrofuran (**4**) on the basis of the following data: mol wt 152 (mass spectrum); ν_{max} 1613 (m), 1130 (s), 1045 (s), 1034 (s), 721 cm^{-1} (s); uv$^{95\%\ EtOH}$ $\epsilon_{220\ m\mu}$ 3580, $\epsilon_{200\ m\mu}$ 12,600; nmr (τ, ppm, CCl_4) 3.87 (0.9 H, doublet, J = 2.5 Hz, vinylic H at C_5), 4.71 (1.1 H, broad doublet, J = 9 Hz, side-chain vinylic H), 5.26 (1.0 H, doublet, J = 2.5 Hz, vinylic H at C_4), 5.43 (1.0 H, doublet, J = 9 Hz, H which is both allylic and geminal to the oxygen), 8.22 and 8.30 (6.0 H, two doublets, both J's = 1 Hz, vinylic methyl H), 8.92 (3.0 H, singlet, methyl H), 9.11 (3.0 H, singlet, methyl H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.04; H, 10.36.

The 11% photoproduct (B) was tentatively identified as *cis*- and *trans*-1,2-epoxy-3-[1′-(2-methylpropenyl)]-4,4-dimethylcyclobutane (**9**) on the basis of the following data: mol wt 152 (mass spectrum), the next peaks were at 137 (m − 15) and 123 (large, m − 29); ν_{max} 1374 (m), 1361 (w), 1326 (m), 943 (w), 839 cm^{-1} (s); nmr (τ, ppm, CCl_4) 4.69–5.07 (1.0 H, broad absorption, vinylic H), 6.30–6.70 (1.5 H, absorption that appeared as a broad singlet at 6.37 and three doublets at 6.54, 6.61 and 6.68, all J's = 2 Hz, epoxy H), 7.55 and 7.64 (0.9 H, two broad doublets, both J's = 9 Hz, allylic H), 8.28 (3.0 H, doublet, J = 1 Hz, vinylic methyl H), 8.45 (2.5 H, doublet, J = 1 Hz, vinylic methyl H), 8.80, 9.02, 9.04, and 9.27 (7.1 H, four singlets, methyl H).

A 100-Mc nmr spectrum showed the vinylic proton as a triplet (separation = 9–10 Hz, probably two overlying doublets), confirmed the assignment for the epoxy protons, showed the allylic proton as a triplet (separation = 8 Hz, two overlying doublets), and confirmed the four methyl singlets as nonequivalent, uncoupled peaks. Irradiation of the vinylic proton collapsed the allylic triplet to a doublet and irradiation of the allylic proton collapsed the vinylic triplet to a broad doublet. Irradiation of the allylic proton definitely changed the pattern for the epoxy proton absorption but did not seem to simplify it.

The 14% photoproduct (C) was identified as *t*-butyl 3,3,6-trimethyl-Δ^5-heptenoate (**7**) on the basis of the following data: mass spectrum, last peak at 170; ν_{max} 1727 (s), 1706 (shoulder, *cis* **1**), 1385 (w), 1362 (m), 1170 (m), 1140 (s), 1115 (m), 978 (w), 962 (w), 881 cm^{-1} (w); nmr (τ, ppm, CCl_4) 4.49–5.01 (1.0 H, broad quartet, separation = 8 Hz, vinylic H), 7.82–8.16 (4.4 H, multiplet with a singlet at 7.97, allylic H and H α to the carbonyl), 8.29 (8.1 H, broad singlet, vinylic methyl H; there was also a smaller broad singlet at 8.40, included in the integration, which was assigned to an impurity), 8.58 (6.8 H, singlet, *t*-butyl H), 9.05 (5.7 H, singlet, methyl H). The nmr spectrum was contaminated with a small amount of *cis* aldehyde **1**, which gave small methyl absorption peaks at 8.68 and 8.79 as well as a small doublet for the aldehydic proton.

A 100-Mc nmr spectrum resolved the vinylic proton quartet into a doublet (τ 4.64, J = 7 Hz, *cis* aldehyde **1**) and a triplet (τ 4.79, J = 7.5 Hz). Also, addition of *cis* **1** to the 60-Mc nmr sample caused the two lower field peaks of the vinylic proton quartet to increase in amplitude.

There was no indication from the nmr spectrum that ester **7** was contaminated with any *trans* aldehyde **1**, although the two compounds were unresolved by vpc. Also, the very rapid decrease of *trans* **1** during the irradiation indicates that it was probably all gone by the end of the irradiation.

Irradiation of 2,2-Dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde-d_1 (2).—A solution of 371 mg of 2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde-d_1 (**2**) (76% *trans*, 20% *cis*, 4% impurity) in 125 ml of *t*-butyl alcohol (0.019 mol) was irradiated for 5.5 hr using Corex-filtered light. The vpc monitor showed that this irradiation exactly paralleled the irradiation of 2,2-dimethyl-3-3[1′-(2-methylpropenyl)]cyclopropylaldehyde (**1**), and the final yields were 51% product A, 10% product B, 10% product C, 4% *cis* **2**, and 25% several minor products and nonmonomeric material:

Product A was 2-[1′-(2-methylpropenyl)]-3,3-dimethyl-5-deuterio-Δ^4-dihydrofuran (**5**): mass spectrum, small peaks at 153 and 138 (m − 15), very large peak at 123 (m − 30); ν_{max} 1585 (s), 1376 (m), 1357 (w), 1193 (m), 1047 (m), 1035 (s), 983 (s), 995 cm^{-1} (m); nmr (τ, ppm, CCl_4) the spectrum was identical with that for undeuterated 2-[1′-(2-methylpropenyl)]-3,3-dimethyl-Δ^4-dihydrofuran (**4**), except that the doublet at 3.87 had disappeared and the doublet at 5.26 had changed to a singlet at 5.26.

Product B was *cis*- and *trans*-1,2-epoxy-2-deuterio-3-[1′-(2-methylpropenyl)-4,4-dimethylcyclobutane (**10**): mass spectrum, a trace peak at 153, peak at 138 (m − 15), peaks at 123 (m − 30) and 124 (m − 29); ν_{max} 1374 (m), 1359 (m), 1309 (m), 913 (w), 909 (m), 702 (w), 694 cm^{-1} (w); nmr (τ, ppm, CCl_4), the spectrum was essentially identical with that for undeuterated 1,2-epoxy-3-[1′-(2-methylpropenyl)]-4,4-dimethylcyclobutane (**9**), except that the absorption for the epoxy protons had changed from a broad singlet at 6.37 and three doublets at 6.54, 6.61 and 6.68 to a singlet at 6.62 and a doublet at 6.66 (J = 2 Hz). There was still some weak absorption at 6.37 which probably was an impurity. Irradiation of the allylic proton collapsed the doublet at 6.66 to a singlet.

Product C was *t*-butyl 3,3,6-trimethyl-4-deuterio-Δ^5-heptenoate (**8**): mass spectrum, a last peak at 171 (no peak at 170); ν_{max} 1727 (s), 1689 (shoulder, *cis* **2**), 1385 (w), 1362 (m), *ca* 1139 (s, broad), 961 (w), 842 cm^{-1} (w); 100-Mc nmr (τ, ppm, CCl_4), the spectrum was essentially identical with that for undeuterated *t*-butyl 3,3,6-trimethyl-Δ^5-heptenoate (**7**), except that the absorption for the vinylic proton had changed from a triplet at 4.79 (J = 7.5 Hz) to a broad doublet at 4.82 (J = 7.5 Hz). Again, the sample was contaminated with *cis* **2** (small doublet at τ 4.64, J = 7 Hz). Addition of *cis* **2** to the nmr sample caused the 4.64 doublet intensity to increase, relative to the doublet at 4.82.

(17) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

Irradiation of 1-Acetyl-2,2-dimethyl-3-[1′-(2-methylpropenyl)]-cyclopropane (3).—A solution of 1.11 g of 1-acetyl-2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropane (**3**) (57% *trans*–43% *cis*; the sample also contained 9% ethyl crysanthemumate and 1% another impurity but these compounds were stable to the irradiation conditions and did not interfere) in 170 ml of *t*-butyl alcohol (0.039 *M*) was irradiated 4 hr using Corex-filtered light. The vpc monitor showed the formation of one major photoproduct with the following percentages at the end of the irradiation: 52% product A (retention time relative to *cis* **3** equaled 0.38), 1% a minor unidentified product (retention time relative to *cis* **3** equaled 0.79), 17% *cis* **3**, 12% *trans* **3** (retention time relative to *cis* **3** equaled 0.96), and *ca.* 18% nonmonomeric material. Also, the monitor showed that *trans* **3** disappeared faster than *cis* **3**.

Solvent was removed and the photoproduct, isolated by vpc of the colorless oil (0.71 g) on a 25% Carbowax 20M column (9 ft × $^3/_8$ in.), was identified as 2-[1′-(2-methylpropenyl)]-3,3,5-trimethyl-Δ^4-dihydrofuran (**6**) on the basis of the following data: mass spectrum, last peak at 166, peaks at 151, 137, 109, base peak at 123; ν_{max} 1672 (s), 1380 (s), 1248 (s), 1009 (s), 948 (s), 735 cm^{-1} (s); uv$^{abs\ EtOH}$ $\epsilon_{220\ m\mu}$ 4620, $\epsilon_{210\ m\mu}$ 7410; nmr (τ, ppm, $CDCl_3$) 4.59 (1.0 H, broad doublet, J = 10 Hz, side chain vinylic H), 5.25 (0.9 H, doublet, J = 10 Hz, H which is both allylic and geminal to the oxygen), 5.45 (0.8 H, broad singlet, vinylic H at C_4), 8.10–8.31 (8.8 H, multiplet, vinylic methyl H), 8.92 and 9.08 (6.5 H, two singlets, methyl H).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.55; Hr, 11.19.

An nmr specrtrum of recovered **3**, vpc collected, showed no indication that any ester photoproduct similar to **7** had been formed.

Irradiation of 2-[1′-(2-Methylpropenyl)]-3,3-dimethyl-Δ^4-dihydrofuran (4).—A solution of 33 mg of **4** in 15 ml of cyclohexane (0.014 *M*) was irradiated in a quartz flask for 0.5 hr using light from a 100-W Hanovia lamp (Model 608A-36). Vpc monitoring of the irradiation showed three photoproducts with retention times relative to starting material of 2.61, 4.31, and 4.97. The final yields were 51% starting material, 3, 4, and 8% photoproducts, in order of glpc elution, and 34% nonmonomeric material. The 4 and 8% products had identical vpc retention times as *trans*- and *cis*-2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde (**1**), respectively. The 3% product was not identified and the irradiation was not investigated further.

Irradiation of **4** with a 450-W lamp (21 mg, 10 ml of cyclohexane, 0.014 *M*, quartz flask, 0.75 hr) resulted in almost complete polymerization of both starting material and photoproducts.

Registry No.—*trans* **1**, 20104-05-6; *cis* **1**, 20104-06-7; *trans* **2**, 20104-07-8; *cis* **2**, 20104-08-9; *trans* **3**, 20104-09-0; *cis* **3**, 20104-10-3; **4**, 20104-11-4; **5**, 20104-12-5; **6**, 20104-13-6; **7**, 20104-14-7; **8**, 20104-15-8; *trans* **9**, 20104-16-9; *cis* **9**, 20104-17-0; *trans* **10**, 20104-18-1; *cis* **10**, 20104-19-2.

Acknowledgment.—The authors would like to thank Mr. P. Porcaro (Givaudan) for aid in some of the analytical work.

The Synthesis of Racemic *threo*- and *erythro*-β-Hydroxylysines

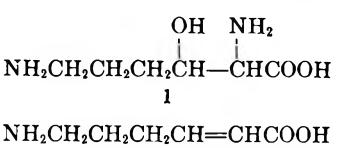
CHARLES H. STAMMER[1] AND RONALD G. WEBB[2]

Department of Chemistry, University of Georgia, Athens, Georgia 30601

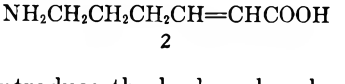
Received December 30, 1968

The synthesis of both *threo*- and *erythro*-β-hydroxy-DL-lysines from an *erythro*-β-methoxy-α-bromohexanoic acid derivative has been accomplished. Amination of this acid in ammonium hydroxide proceeded with retention while treatment with sodium azide proceeded with inversion of the configuration at the α-carbon atom giving intermediates convertible into the two diastereomeric amino acids.

In connection with our program on the synthesis of cycloserines, the unknown β-hydroxylysine (**1**) was a required intermediate. β-Hydroxyamino acids have been synthesized in the past by (1) the condensation of acid chlorides with diazoacetates and azlactones followed by several steps,[3] (2) condensation of aldehydes with glycine[4] and esters of acetamidomalonic and nitroacetic acids, and (3) multistep formation of the α-amino-β-hydroxy structure from the appropriate α,β-unsaturated acid.[5] After several attempts to use the second method, the longer surer approach through the α,β-unsaturated acid led to the desired compound. In this reaction sequence, a 6-amino-2-hexenoic acid (**2**) derivative was required which could be converted into **1** by the introduction of the appropriate functional groups. Two stereoisomers of **1** are possible and it was



1



2

desirable to introduce the hydroxyl and amino groups stereospecifially so that both the *threo* and *erythro* isomers would both be available.

The synthesis of **2** appeared feasible by the Doebner condensation[6] of an N-substituted γ-aminobutyraldehyde with malonic acid. The problem, then was to synthesize the required aldehyde. N-Benzoyl-γ-aminobutyraldehyde had been reported as quite unstable,[7] possibly owing to a tendency toward ring closure giving a pyrrolidine. Attempts to prepare N-benzoyl-γ-aminobutyric acid chloride had indeed led to the ring-closed product, N-benzoyl-2-pyrrolidone. Consequently, it seemed necessary to block the amino function with a group such as phthaloyl which would effectively pro-

(1) To whom inquiries should be addressed.

(2) Taken from the Ph.D. Thesis of R. G. Webb which was presented to the University of Georgia Graduate School, Oct 1968.

(3) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957); H. E. Carter, J. B. Harrison, and D. Shapiro, *J. Amer. Chem. Soc.*, **75**, 4705 (1953); J. M. Stewart and D. W. Wooley, *ibid.*, **78**, 5336 (1956).

(4) T. Wieland, H. Cords, and E. Keck, *Ber.*, **87**, 1312 (1954); T. T. Otani and M. Winitz, *Arch. Biochem. Biophys.*, **102**, 464 (1963); M. Sato, K. Okawa, and S. Akabori, *Bull. Chem. Soc. Jap.*, **30**, 937 (1957); H. Mix and F. W. Wilcke, *Z. Physiol. Chem.*, **337**, 40 (1964); H. Hellmann and H. Piechota, *ibid.*, **318**, 66 (1960); H. Hellmann and H. Piechota, *Ann. Chem.*, **631**, 175 (1960); S. Umezawa and S. Zen, *Bull. Chem. Soc. Jap.* **36**, 1143 (1963); D. I. Weisblatt and D. A. Lyttle, U. S. Patent 2,570,297 (1951).

(5) (a) W. Schrauth and H. Geller, *Chem. Ber.*, **55**, 2783 (1922); (b) H. D. West and H. E. Carter, *J. Biol. Chem.*, **119**, 103 (1937); (c) H. D. West, G. S. Krummel and H. E. Carter, *ibid.*, **122**, 605 (1937); (d) H. E. Carter and C. L. Zirkle, *ibid.*, **178**, 709 (1949); (e) K. Pfister, III, E. E. Howe, C. A. Robinson, A. C. Shabica, E. W. Pietrusza, and M. Tishler, *J. Amer. Chem. Soc.*, **71**, 1096 (1949); (f) T. Kanebo and H. Katsura, *J. Chem. Soc. Jap.* **36**, 899 (1963).

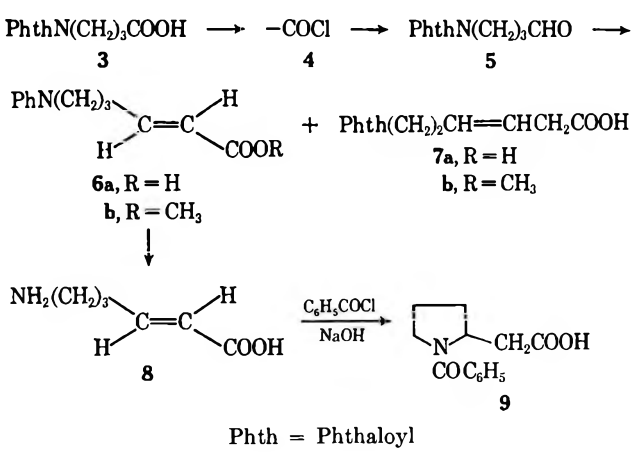
(6) J. R. Johnson, *Org. Reactions*, **1**, 226 (1942).

(7) S. Sugasan and Y. Zusshi, *J. Pharm. Soc. Jap.*, **550**, 1044 (1927).

hibit reactions at that site. N-Phthaloyl-γ-aminobutyric acid (**3**) was readily prepared by treating γ-aminobutyric acid directly with phthalic anhydride as previously described.[8] This acid was readily converted into the known acid chloride (**4**) which could be reduced without purification by the Rosenmund[9] procedure to the desired N-phthaloyl-γ-aminobutyraldehyde (**5**). The reduction proceeded under scrupulously dry conditions to evolve *ca.* 80% of the theoretical yield of hydrogen chloride using a $Pd/BaSO_4$ catalyst and afforded an acceptable yield of crude aldehyde. Many purification methods including recrystallization, chromatography, bisulfite adduct formation, conversion into the aldehyde diacetate, etc., gave aldehyde of variable purity. Finally, an acceptably pure material, which afforded a 2,4-dinitrophenylhydrazone of correct melting point,[10] was obtained by short-path vacuum distillation in about 50% yield. Either the crude or the purified aldehyde could be used in the next step with good results.

Doebner condensation (Chart I) of the aldehyde with malonic acid gave a product which by all indications was a mixture of acids. Extraction of the crude product

CHART I

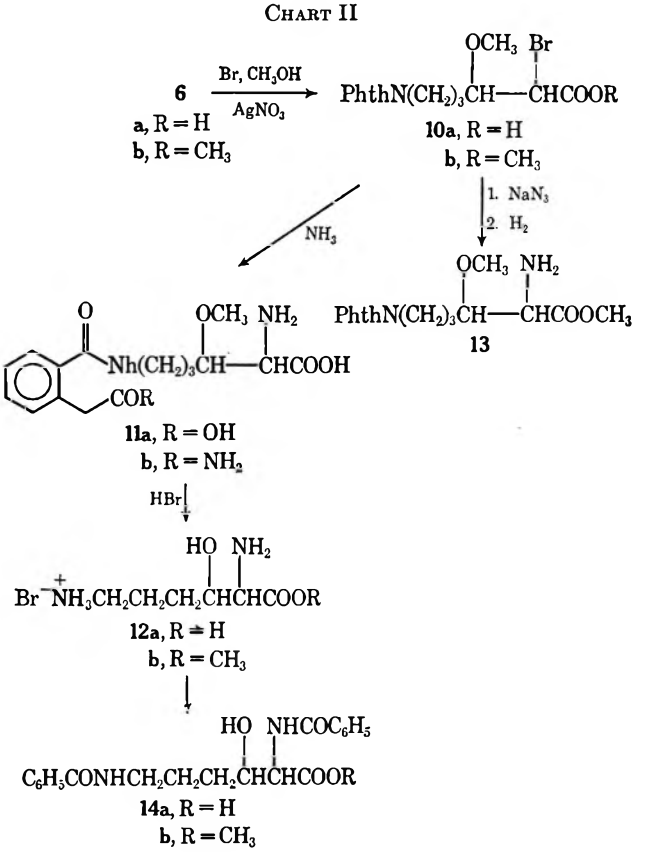


Phth = Phthaloyl

with successive portions of hot water separated it into a low-melting (126–127°) more soluble material and a high-melting (153–156°) less soluble product. The latter was shown to be the expected *trans*-6-phthalimido-2-hexenoic acid (**6a**) while the former **7a** was thought to be the *cis* isomer. Attempts to convert this low-melting product into **6a** by known isomerization procedures, *i.e.*, irradiation in the presence of iodine and melting in the presence of iodine, gave mixtures of **6a** and **7a**. It was found that dephthaloylation of **6a** gave the crystalline amino acid **8** which showed a vinylic coupling constant consistent with the *trans* configuration in its nmr spectrum, as did that of the parent **6a**. When an attempt was made to benzoylate **8** under Schotten–Baumann conditions, only **9** (N-benzoylpyrrolidine-2-acetic acid) was obtained, resulting from an internal Michael addition of the ω-amino group to the α,β-unsaturated system[11] followed by benzoylation. If the low-melting compound (**7a**) were the *cis* isomer of **6a** it should undergo this same series of reactions resulting in the formation of **9**. A low yield of **9** was actually obtained from **7a** but a definite structural assignment was not possible. Esterification of the low-melting isomer in boiling methanolic hydrogen chloride gave a considerable amount of the highly insoluble *trans* methyl ester (**6b**) and **7b**, the methyl ester of **7a**. Its nmr spectrum showed clearly the α-methylene doublet and a complex multiplet in the vinyl region as would be expected of the β,γ-unsaturated ester. The esterification process allowed a separation of **6a** and **7a** owing to a difference in solublility of the methyl esters. It was clear also that **7** was being partially converted into **6** under the acid conditions of the esterification. Diazomethane esterification of both **6a** and **7a**, however, gave noncrystalline products of indeterminate structure.

The *trans* acid (**6a**), now in hand, was converted into α-bromo-β-methoxy-ω-phthalimidohexanoic acid (**10a**) by the method of Carter[5c] (Chart II). This compound

CHART II



was difficult to purify and molecular distillation followed by recrystallization was used to obtain an analytical sample. Attempts to make the simple α-bromo-β-hydroxy analog of **10a** by the addition[5d] of HOBr to **6a** give only unchanged starting material. Amination of the crude bromoethoxy compound (**10a**) in concentrated ammonium hydroxide gave a product showing two or three ninhydrin positive spots. The multiplicity of spots was probably due to the formation of ring-opened phthalamic acids (**11a** and **11b**), since it is well

(8) S. Gabriel and J. Coleman, *Chem. Ber.*, **41**, 513 (1908); J. H. Villman and W. F. Harting, *J. Amer. Chem. Soc.*, **70**, 1473 (1948); see also R. Laliberté and L. Berlinguet, *Can. J. Chem.*, **38**, 1933 (1960).

(9) E. Mosettig and R. Mozingo, *Org. Reactions*, **4**, Chapter 7 (1948).

(10) K. Balenovic, I. Jambresic, and I. Furic, *J. Org. Chem.*, **17**, 1459 (1952).

(11) B. R. Baker, R. E. Schaub, and J. N. Williams, *ibid.*, **17**, 124 (1952).

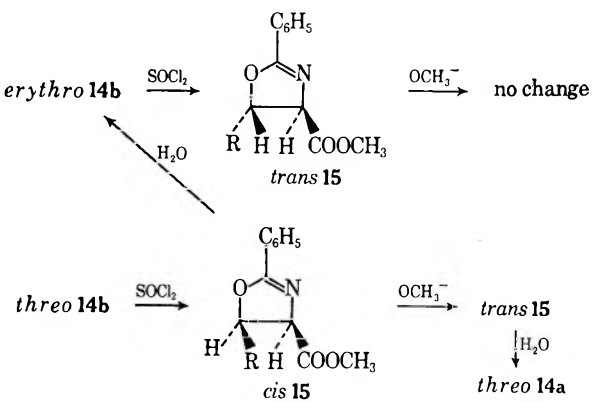
known that phthalimide derivatives are very sensitive to base.[12] The crude phthalamic acid mixture was hydrolyzed without separation in refluxing 48% hydrobromic acid. Paper chromatographic analysis of the hydrolysis reaction mixture showed that the phthaloyl group was removed in less than 1 hr, while 4-hr reflux gave the best yield of the demethylated amino acid (**12**). The product was isolated after conversion into the monohydrobromide salt with pyridine and the monohydrobromide was convertible into the monohydrochloride by passage through IRA-400 on the chloride cycle. Dissatification with the losses involved in the purification of the bromomethoxy acid (**10a**) led us to study a number of alternate methods for the addition of methyl hypobromite and of hypobromous acid to **6a** and its methyl ester. N-Bromosuccinimide (NBS) in aqueous dimethyl sulfoxide and dimethoxyethane gave essentially unreacted acid as did N-bromoacetamide (NBA). The methyl ester (**6b**), however, gave reasonable yields of bromomethoxy ester (**10b**) when it was treated with bromine in a methanolic silver nitrate solution. Methanolic NBS and NBA in the presence of hydrogen bromide or hydrogen chloride also gave **10b** in somewhat lower yields.

The addition of the elements of methyl hypobromite to α,β-unsaturated acids has been shown to occur both regiospecifically[13] and stereospecifically[5c,e] by its addition to crotonic (*trans*) and isocrotonic (*cis*) acids to give allothreonine (*erythro* configuration) and threonine (*threo* configuration), respectively. We could, consequently, assign the *erythro* configuration to **10a** by analogy with this early work. We showed that the ester obtained by the bromomethoxylation of ester **6b** was the same **10b** obtained when the acid **10a** was esterified. Thus, the regio- and stereospecificity of the bromomethoxylation was unaffected by esterification of the **6a** carboxyl function. Amination of **10a** with ammonia should, by analogy with Pfister's work on threonine,[14] be accomplished with retention of configuration at the α-carbon atom giving the acid **11** with an *erythro* configuration. Our amino acid (**12a**) derived from **11** could thus be assigned the *erythro* configuration.

When the ester **10b** was treated with sodium azide in dimethyl sulfoxide solution[15] followed by reduction of the intermediate azide ester, a β-methoxylysine ester (**13**) was obtained. Since the reaction of the halo ester with azide ion is known[16] to invert the configuration of the α-asymmetric center, the lysine derivative **13** had the *threo* configuration and was diastereomeric with **11** and **12a** prepared earlier. In spite of this, hydrolysis of **13** gave an amino acid having the same R_f values as **12a** in three paper chromatography systems. However, both the acid hydrobromides and corresponding methyl ester hydrochlorides were shown to be different by infrared and nmr spectral comparison. The *erythro* isomer showed an unexpected resistance to esterification by the usual methods, *i.e.*, dry HCl/CH_3OH or dimethyl sulfite–methanol, and **12b** was obtained in only 15% yield. The *threo* ester, however, was isolated in 78% yield using the standard HCl/CH_3OH procedure. For further comparison, the N,N′-dibenzoyl derivatives (**14a**) of both isomers were synthesized and the comparison of these again showed that the two amino acids were indeed isomeric.

Confirmation of both the structural and stereochemical assignments made above was obtained by physical and chemical means. An nmr study of both *erythro* **12** and *threo* **12** as their monohydrobromide salts showed that the doublet characteristic of the α proton shifted 0.54 ppm upfield when the pH was increased, while the multiplet absorption for the β proton shifted only 0.32 ppm. Deprotonation of the ammonium ion must be responsible for the greater diamagnetic shift of the α proton since the carboxyl function was ionized both before and after the pH increase. These data support the α-amino-β-hydroxy structure. Substantiation of the configurations assigned was obtained by use of the well-known[17] oxazoline method. This method is based on the known steric course of oxazoline formation from α,β-amino alcohols and the fact that *cis*-4,5-disubstituted 2-oxazolines isomerize to the *trans* isomers under basic conditions. This reaction sequence involving the new hydroxylysines is shown in Chart III. Treatment

CHART III



of the dibenzoyl esters (**14b**) of the isomeric amino acids with thionyl chloride converted each into a 2-oxazoline. This process is known to occur with inversion of configuration at the β-carbon atom[17b,c] requiring that the *erythro* isomer should form the *trans*-4,5-disubstituted oxazoline (*trans* **15**) and the *threo* isomer should give *cis* **15**. *trans* **15**, formed from *erythro* **14b**, was in fact an oil which was unchanged upon treatment with methanolic sodium methoxide as shown by solution infrared. *cis* **15**, as prepared from the *threo* isomer, was a crystalline solid whose nmr spectrum showed a coupling of 9 Hz between the 4 and 5 protons, consistent with the *cis* configuration. When *cis* **15** was treated with methanolic sodium methoxide it isomerized to

(12) L. R. Caswell, P. L. Wright, and D. D. Adams, *Texas J. Sci.*, **17**, 334 (1965); L. R. Caswell and P. C. Atkinson, *J. Org. Chem.*, **29**, 3151 (1964).

(13) This term refers to the *direction* of methyl hypobromite addition, *i.e.*, α-bromo-β-methoxy *vs.* α-methoxy-β-bromo; *cf.* A. Hassner, *ibid.*, **33**, 2684 (1968).

(14) According to early work on the amination of α-bromo acids, β-substituted α-bromo acids undergo amination with retention of configuration, while β-unsubstituted α-bromo acids aminate with inversion. A modern study of these reactions has apparently not been done. For a complete discussion of this, see J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol 1, John Wiley & Sons, Inc., New York, N. Y., 1961, pp 165–167.

(15) R. A. Strojny and H. C. White, *J. Org. Chem.*, **28**, 1942 (1963).

(16) P. Brewster, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, **166**, 178 (1950).

(17) (a) M. Pankova and J. Sicher, *Collect. Czech. Chem. Commun.*, **30**, 388 (1965); (b) A. F. Wagner, *J. Amer. Chem. Soc.*, **79**, 3240 (1957); (c) J. M. Stewart, *ibid.*, **83**, 435 (1961); (d) D. F. Elliot, *J. Chem. Soc.*, (1949); (e) D. F. Elliot, *ibid.*, 62 (1950); (f) W. S. Johnson and E. N. Schubert, *J. Amer. Chem. Soc.*, **72**, 2187 (1950); (g) S. H. Pines, S. Karaday, M. A. Kozlowski, and M. Sletzinger, *J. Org. Chem.*, **33**, 1762 (1968).

trans **15** which (without isolation) was hydrolyzed to the *threo*-dibenzoyl acid (*threo* **14a**) almost quantitatively. Since hydrolysis of 2-oxazolines does not change the configurations of the asymmetric centers, the formation of the *threo*-amino acid proved that *cis* **15** had been isomerized by the methoxide treatment. Indeed, hydrolysis of *cis* **15** without prior base treatment gave *erythro* **14a** showing that a single inversion had occurred during the thionyl chloride reaction.

Our work thus confirmed earlier reports that amination of β-substituted α-bromo acids proceeded with retention of configuration while azide displacement gave the diastereomeric configuration. The stereospecificity of these reactions can be used to allow the synthesis of both isomers of a given amino acid from a single bromo acid intermediate. Consequently, the use of an α,β-unsaturated acid of known configuration and its subsequent bromomethoxylation becomes an attractive method for the synthesis of *both* diastereomers of any desired β-hydroxyamino acid.

Experimental Section

All melting points were determined using the capillary method and are uncorrected. Petroleum ether refers to a 30–60° boiling fraction. For circular paper chromatography, Whatman No. 1 paper (32-cm diameter with a 2-cm center hole) was used. BAW is the upper phase which separates when *n*-butyl alcohol, acetic acid, and water are mixed in a volume ratio of 5:1:4, respectively; PW is a 65:35 mixture of pyridine and water; MPW is a 20:5:8 mixture of methyl ethyl ketone, pyridine, and water. The amino acids were visualized with ninhydrin reagent. The infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 or Model 237B using a polystyrene standard. The nmr spectra were obtained on a Varian A-60 or HA-100 instrument with TMS (tetramethylsilane) as standard except in D_2O where TMS*, 3-(trimethylsilyl)propanesulfonic acid sodium salt, was used. The majority of the nmr spectra were calibrated by the usual techniques. All elemental analyses were performed by Midwest Microlab, Indianapolis, Ind.

γ-Phthalimidobutyraldehyde (5).—When 16.5 g (0.066 mol) of γ-phthalimidobutyryl chloride (**4**) was reduced under Rosenmund conditions[9] (Quinoline-S poison was unnecessary), 15.4 g of a gummy product was obtained. After sublimation *in vacuo* at 90–120° for 50–60 hr, 7.7 g (37%) of **5** was obtained: mp 69–72° (lit.[10] mp 72–73°); ir (Nujol) 1770 (imide C=O), 1706 (imide C=O), 1315, 1125, 1050, and 860 cm^{-1}; nmr ($CDCl_3$) δ 7.74 (m, C_6H_4), 3.75 (t, N-CH_2), 2.25 (m, α,β-CH_2CH_2), 9.75 (s, CHO). The 2,4-dinitrophenylhydrazine derivative had mp 184–185° (lit.[18] mp 185°).

6-Phthalimido-2-hexenoic Acid (6a).—A solution of 72.5 g (0.3 mol) of γ-phthalimidobutyraldehyde or an equivalent amount (based on HCl evolution) of crude aldehyde and 62.5 g (0.6 mol) of malonic acid in 150 ml of pyridine was heated for 12–24 hr in an oil bath at 65–86° until evolution of CO_2 ceased. The cooled solution was diluted with five volumes of water and 10% sulfuric acid was added until no more oil or solid formed. The supernate was decanted and the product was washed twice with water and recrystallized from 50% ethanol, mp 115–140°. This material was further recrystallized from 2-propanol and then from ethanol giving 12.7 g (15%): mp 153–155°; ir (Nujol) 1770 (imide C=O), 1725 (acid C=O), 1695 (imide C=O), 1670, 1631 cm^{-1}; nmr (DMSO-d_6) δ 7.76 (m, C_6H_4), 3.54 (t, NCH_2), 1.90 (m, γ, δ-CH_2CH_2–), 6.8 (pentuplet, $J_{\alpha,\beta}$ = 16 Hz, $J_{\beta,\gamma}$ = 6 Hz, –CH_2CH=CH), 5.73 (d, J = 16 Hz, CH=CHCOOH). The analytical sample was obtained by recrystallization of a portion of this material from ethanol, mp 156–158°.

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.92; H, 5.25; N, 5.46.

6-Amino-*trans*-2-hexenoic Acid Hydrochloride (8).—6-Phthalimido-2-hexenoic acid (**6a**, 3.3 g, 12.8 mmol) was dissolved in 30 ml of 1 *N* NaOH and allowed to stand at room temperature for 30 min. The addition of 4.3 ml (52 mmol) of concentrated HCl caused a precipitate to form which dissolved when the mixture was refluxed for 1 hr. The solution was cooled in ice and the precipitated phthalic acid (89%) was removed by filtration. The remaining solution was evaporated under vacuum and held at oil-pump vacuum overnight. The resulting solid was extracted with two 25-ml portions of boiling ethanol leaving behind 1.6 g of sodium chloride. The ethanol extract was evaporated to give 2.2 g solid, mp 140–155°, which was recrystallized from 40 ml of isopropyl alcohol, giving 1.3 g of product: mp 150–157°; ir (Nujol) 3100, 1700 (acid C=O), 1645, C=C), 980 cm^{-1} (*trans* C=C; nmr (D_2O) δ 3.05 (t, NCH_2), 1.90 (m, δ-CH_2), 2.32 (t, CH_2CH=CH), 7.05 (two t, $J_{\alpha,\beta}$ = 16 Hz, $J_{\beta,\gamma}$ = 7 Hz, CH_2-CH=CH), 5.95 (d, J = 16 Hz, CHCOOH); MPW, R_f 0.35 (blue); PW, R_f 0.70 (pink); BAW, R_f 0.62 (pink). The analytical sample was obtained by two crystallizations from ethanol, mp 156–159°.

Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; Cl, 21.41; N, 8.46. Found: C, 43.26; H, 7.25; Cl, 21.12; N, 8.49.

N-Benzoylpyrrolidine-2-acetic Acid (9).—A sample of 6-amino-*trans*-2-hexenoic acid hydrochloride (**8**) was benzoylated according to Baker[11] giving a crystalline product, mp 134° (lit.[11] mp 134°). Paper chromatography of a basic aqueous solution of the amino acid **8** (MPW, R_f 0.35, blue spot) showed an immediate change to the pyrrolidine acetic acid (MPW, R_f 0.39, yellow spot) before benzoylation.

Methyl 6-Phthalimido-2-hexenoate (6b).—6-Phthalimido-2-hexenoic acid (**6a**, 35.1 g, 10.13 mol) was dissolved in 350 ml of methanol and the solution was saturated with hydrogen chloride without external cooling and then refluxed 1 hr. On cooling the solution to room temperature, the ester crystallized and was collected and washed with cold methanol: weight 22.7 g (61%); mp 90–92°, ir (Nujol) 1775 (imide C=O), 1720 (ester C=O), 1705 cm^{-1} (imide C=O); nmr ($CDCl_3$) δ 7.75 (m, C_6H_4), 3.70 (t, NCH_2–), 2.08 (m, γ, δ-CH_2CH_2–), 6.94 (two t, $J_{\alpha,\beta}$ = 15 Hz, $J_{\beta,\gamma}$ = 7 Hz, CH_2CH=CH), 5.80 (d, J = 15 Hz, CH=CH-$COOCH_3$), 3.65 (s, $COOCH_3$). A second crop of 6.3 g, mp, 82–84°, was obtained on cooling the mother liquor.

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.74; H, 5.74; N, 5.30.

***erythro*-α-Bromo-β-methoxy-ε-phthalimidocaproic Acid (10).**—From a dropping funnel, 72.3 g (0.28 mol) of 6-phthalimido-2-hexenoic acid (**6a**) in 1100 ml of methanol was added over 1.5 hr to a rapidly stirred suspension of 46.8 g (0.28 mol) of silver nitrate in 750 ml of methanol in a 3-l. ice-cooled beaker. Concurrently 15.2 ml (0.28 mol) of bromine was bubbled into the solution in a stream of air. After stirring an additional 2 hr in ice the mixture was filtered and evaporated under vacuum giving 101.2 g of red oil. The residue was dissolved in about 1 l. of ether, and the solution was washed with three 500-ml portions of water. After drying over sodium sulfate, the solution was evaporated to dryness giving 77.7 g of light yellow oil. After three crystallizations of 1.2 g of the crude oil from 10, 3.5, and 5 ml of benzene, 0.58 g of material, mp 108–116°, was obtained. Molecular distillation of 200 mg of this product at 0.01 mm and 160° gave 0.174 g of analytical sample: mp 115–118°; ir (Nujol) 1758, 1710 cm^{-1} (acid C=O); nmr ($CDCl_3$) δ 7.76 (m, C_6H_4), 4.15 (d, J = 8 Hz, α proton), 3.68 (t, NCH_2–), 3.38 (s, OCH_3), 1.80 (m, γ, δ-CH_2CH_2–).

Anal. Calcd for $C_{15}H_{16}BrNO_5$: C, 48.66; H, 4.36; Br, 21.59; N, 3.78. Found: C, 48.88; H, 4.53; Br, 21.63; N, 3.55.

***erythro*-β-Hydroxy-DL-lysine Hydrobromide (*erythro* 12a).**—Crude α-bromo-β-methoxy-ε-phthalimidocaproic acid (**10a**, 74 g) was divided into four approximately equal portions and placed in four 500-ml hydrogenation bottles. Concentrated ammonium hydroxide (300 ml) was added to each, a rubber stopper was securely wired in place, and the bottles were stored in an oven at 50° for 3.5 days. After cooling in ice, the solutions were filtered and the combined filtrates were evaporated under vacuum. The crude α-amino-β-methoxy-ε-phthalimidocaproic acid–ammonium bromide mixture was a yellow glass (79 g). Paper chromatography of this material showed the following ninhydrin positive materials: MPW, R_f 0.14, BAW, R_f 0.30, 0.46, 0.59.

The crude α-amino-β-methoxy-ε-phthalimidocaproic acid (70.8 g) was treated with 470 ml of refluxing 48% hydrobromic acid for 4 hr. The hydrobromic acid was evaporated under vacuum, 200 ml of water was added to the residue, and 18.5 g of phthalic acid was collected by filtration. The filtrate was treated with Norit and evaporated under vacuum, and the solid residue was dissolved in 40 ml of hot water. Pyridine (28 ml) was added and,

(18) F. E. King, P. L'Ecuyer, and H. T. Openshaw, *J. Chem. Soc.*, 1477 (1933).

after cooling to room temperature, the solution was filtered. The filtrate was heated, 800 ml of hot ethanol was added, and the solution was filtered and allowed to cool. After standing at 0° overnight, 14.0 g of crude β-hydroxylysine hydrobromide was collected on a filter. This was dissolved in 14.0 ml of hot water, and 35 ml of hot ethanol was added in portions. At the cloud point, an oil formed which was separated. The supernate was cooled to −5° overnight and deposited 4.3 g of white solid, mp 224° dec. The separate oil was diluted with 15 ml of ethanol and scratched with a glass rod until crystalline (3.6 g). The spectral properties of these two materials were identical: ir (Nujol) 3450 (OH), 1670, 1590 (COO^-), 1490 cm^{-1} (NH_3^+); nmr (D_2O) δ 4.62 (m, 1, β proton), 4.37 (d, 1, J = 4 Hz, α proton), 3.56 (t, 2, NCH_2–), 2.15 (m, 4, γ, δ-CH_2CH_2–); MPW, R_f 0.13; BAW, R_f 0.28.

The analytical sample was the product which melted at 224° with decomposition.

Anal. Calcd for $C_6H_{15}BrN_2O_3$: C, 29.63; H, 6.22; Br, 32.87; N, 11.52. Found: C, 29.53; H, 6.41; Br, 32.70; N, 11.38.

The hydrochloride of *erythro* **12** could be prepared from the above hydrobromide by passing a sample through an IRA-400 ion exchange column: mp 227° dec; MPW, R_f 0.22.

A dihydrochloride was obtained when the monohydrochloride was treated with 3 *N* HCl followed by a crystallization from methanol–ether, mp 194° dec.

Methyl *erythro*-β-Hydroxylysinate Dihydrochloride (*erythro* 12b).—The monohydrobromide of *erythro*-β-hydroxylysine (*erythro* **12a**, 0.702 g, 2.89 mmol) was converted in aqueous solution into the nitrate by addition of silver nitrate (0.46 g, 2.93 mmol). The precipitated silver bromide was filtered, and the filtrate was evaporated to a yellow oil. The oil was dissolved in a methanolic solution of dimethyl sulfite prepared from 0.32 ml (4.5 mmol) of thionyl chloride and allowed to stand overnight at room temperature. Evaporation of the methanol and reconcentration several times with fresh solvent left an oil. This oil was dissolved in methanol and the solution was saturated with HCl gas and refluxed 15 min. The oil which resulted from removal of the solvent gave crystals from methanol–ether (0.12 g), and the product was recrystallized from 1.2 ml methanol and 5 ml ether giving an analytical sample: 0.105 g (15%); mp 184–186° dec; ir (Nujol) 3370, 1740 ($COOCH_3$), 1235, and 1050 cm^{-1}; nmr (D_2O) δ 4.10 (d, J = 2.5 Hz, α proton), 3.94 (m, β proton), 3.70 (s, $COOCH_3$), 2.90 (m, NCH_2–), 1.67 (m, γ, δ-CH_2CH_2); MPW, R_f 0.54; BAW, R_f 0.37 (pink); PW, R_f 0.83 (pink).

Anal. Calcd for $C_7H_{18}Cl_2N_2O_3$: C, 33.74; H, 7.28; N, 11.24. Found: C, 33.46; H, 7.43; N, 11.39.

***erythro*-N,N′-Dibenzoyl-β-hydroxylysine (*erythro* 14a).**—Schotten–Baumann benzoylation of 595 mg of *erythro* **12a** gave 787 mg (86%) of crude product, mp 162–166°. Recrystallization from 40% aqueous ethanol gave an analytically pure sample: mp 166–167°; ir (Nujol) 3375 and 3280 (NH), 1720 (acid C=O), 1680 (amide C=O), 1635, 1545 and 1250 cm^{-1}; nmr (DMSO-d_6) δ 8.50 (m, C_6H_5CONH), 7.94 (m, C_6H_5, α-benzamido), 7.56 (m, C_6H_5, ε-benzamido).

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.84; H, 5.99; N, 7.56. Found: C, 64.84; H, 6.44; N, 8.06.

Methyl *erythro*-ε-Phthalimido-α-bromo-β-methoxycaproate (10b).—Methyl 6-phthalimido-2-hexenoate (**6b**, 22.5 g, 82.4 mmol) was suspended in 138 ml of ice-cooled methanol and 14.8 g (83 mmol) of N-bromosuccinimide was added in one portion. After stirring for 5 min, 1.4 ml of methanol which had been saturated with hydrogen bromide gas at 0° was added to the suspension. The solution immediately turned orange. After 1 hr the mixture was taken out of the ice bath and allowed to come to room temperature for 1 hr. It was then heated and stirred at no more than 35–40° while all of the solid dissolved to give a clear red solution which was allowed to stand for an additional 5 hr at room temperature. After filtering a trace of solid, the solution was stored in the cold overnight. The solution and the precipitate which had formed were stirred in an ice bath for 5 hr to complete the crystallization. After filtration and drying, 20.8 g of solid was obtained, mp 73–75°. The crude product was recrystallized from 50 ml of methanol: 19.0 g (60%): mp 72–75°; ir (Nujol) 1770 (imide C=O), 1735 (ester C=O), 1720 (imide C=O), and 1395 cm^{-1}; nmr ($CDCl_3$) δ 7.80 (d, phthaloyl phenyl), 4.20 (d, J = 9 Hz, α-H), 3.80 (s, $COOCH_3$), 3.40 (s, methyl ether), 1.83 (m, γ δ-CH_2CH_2).

Anal. Calcd for $C_{16}H_{18}BrNO_5$: C, 50.01; H, 4.72; Br, 20.80; N, 3.65. Found: C, 49.93; H, 4.74; Br, 21.07; N, 3.73.

Methyl *threo*-Nω-Phthaloyl-β-methoxylysinate Hydrochloride (13).—After dissolving 6.5 g (100 mmol) of sodium azide in 83 ml of dimethyl sulfoxide, 18.9 g (49 mmol) of methyl ε-phthalimido-β-methoxy-α-bromocaproate (**10b**) was added with stirring. After the solid dissolved, the solution was kept at 65° for 8 hr. The solution was diluted with water and the resulting precipitated yellow oil was extracted with three 50-ml portions of chloroform. The combined chloroform extracts were washed with 100 ml of water, dried (Na_2SO_4), and evaporated under vacuum. After 1 hr at oil-pump vacuum, 17.8 g of crude methyl ε-phthalimido-β-methoxy-α-azidocaproate was obtained as a light yellow oil: ir (neat) 2100 (N_3), 1745 (ester C=O), and 1770, 1710 cm^{-1} (imide C=O); nmr ($CDCl_3$) δ 3.40 (s, OCH_3), (s, $COOCH_3$) 7.64 (m, phenyl). The azide was dissolved in 100 ml of methanol contained in a 500-ml round-bottomed flask cooled in an ice bath. The catalyst (1.2 g of 5% palladium on carbon) was added as a slurry in 75 ml of methanol, and a slow stream of hydrogen was bubbled through the magnetically stirred solution. After adding 4.1 ml (49 mmol) of concentrated HCl, the ice bath was removed and the solution was allowed to come to room temperature. The course of the reaction was followed by periodically removing a small sample of the reduction mixture and determining the ir spectrum of the products after filtration and evaporation. The azide absorption at 2100 cm^{-1} completely disappeared after 22 hr. The solution was filtered, evaporated under vacuum, and the 15.8 g of yellow glass was dissolved in 38 ml of methanol and slowly diluted with 100 ml of ether. After crystallization was induced by scratching, 100 ml of ether was added and the mixture was kept in the cold. Filtration and drying under vacuum at 46° gave 10.9 g (63%) of **13**: mp 164–166° dec; ir (Nujol) 1765 (imide C=O), 1735 (ester C=O), 1710 (imide C=O), 1395 cm^{-1}; nmr (D_2O) δ 3.52 (s, methyl ether), 3.97 (s, methyl ester), 4.33 (d, J = 4 Hz, α proton), 7.87 (s, phenyl); MPW, R_f 0.98; BAW, R_f 0.78; PW, R_f 0.99.

The analytical sample was obtained by recrystallization from methanol–ether, mp 166–167° dec.

Anal. Calcd for $C_{16}H_{21}ClN_2O_5$: C, 53.85; H, 5.93; Cl, 9.94; N, 7.85. Found: C, 54.00; H, 6.05; Cl, 10.14; N, 7.98.

***threo*-β-Hydroxylysine Hydrobromide (*threo* 12a).**—Methyl Nω-phthaloyl-β-methoxylysinate hydrochloride (**13**, 10.2 g, 28.6 mmol) was refluxed with 42 ml of 48% HBr for 4 hr and the solution was allowed to stand at room temperature overnight. The clear supernate was decanted from the precipitated phthalic acid and the filtrate was extracted with four 50-ml portions of ether to remove dissolved phthalic acid. The aqueous layer was evaporated *in vacuo* giving an oil which was evaporated three times with 50 ml of acetone and twice with 50 ml of benzene. The resulting red oil, after pumping, was dissolved in 70 ml of hot ethanol, and 20 ml of pyridine was added to the hot solution. An oil separated which became granular after refluxing the solution for 5 hr. After filtration and drying, 5.6 g (80%) of light brown solid was obtained: mp 211° dec; ir (Nujol) 3085 (NH_3^+), 1625, 1575 cm^{-1}; nmr (D_2O) δ 4.60 (m, 1, β-H), 4.17 (d, 1, J = 5 Hz, α-H), 3.5 (t, 2, NCH_2–), 2.24 (m, 4, γ, δ-CH_2CH_2–); MPW, R_f 0.17; BAW, R_f 0.16; PW, R_f 0.48.

An analytical sample was obtained by crystallization of the crude *threo*-β-hydroxylysine hydrobromide from aqueous ethanol, mp 218–222° dec.

Anal. Calcd for $C_6H_{15}BrN_2O_3$: C, 29.63; H, 6.22; Br, 32.87; N, 11.52. Found: C, 29.35; H, 6.15; Br, 32.76; N, 11.73.

***threo*-N,N′-Dibenzoyl-β-hydroxylysine (*threo* 14a).**—Schotten–Baumann benzoylation of 0.21 g of crude *threo* **14a** gave 141 mg (64%) of product, mp 167–169°. Recrystallization from aqueous ethanol afforded an analytical sample: mp 167–168°; ir (Nujol) 3480, 3375 (shoulder), 3310, 1715 (acid C=O), 1630 cm^{-1} (amide C=O's); nmr (DMSO-d_6) δ 7.94 (m, C_6H_5, α-benzamide), 7.52 (m., C_6H_5, ε-benzamide).

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.84; H, 5.99; N, 7.56. Found: C, 64.84; H, 6.32; N, 7.81.

Methyl *threo*-β-Hydroxylysinate Dihydrochloride (*threo* 12b).—A suspension of the *threo* acid (*threo* **12a**) (0.53 g, 2.2 mmol) in 50 ml of methanol was saturated with HCl gas and allowed to stand 24 hr. The solvent was evaporated and the residue was dissolved in 2 ml of methanol and precipitated by the addition of ether giving 0.55 g of crude ester, mp 178–179° dec. The crude ester was redissolved in 10 ml of methanol, and after saturation with HCl gas the solution was allowed to stand 24 hr. It was then refluxed 1 hr, cooled, and centrifuged giving 0.43 g (78%) of analytically pure product: mp 189–191° dec; ir (Nujol) 3375, 1740 (ester C=O), 1235, and 1025 cm^{-1}; nmr (D_2O) δ

1.76 (m, γ, δ-CH_2CH_2), 4.32 (d, J = 3 Hz, α-H), 4.25 (m, β-H), 3.86 (s, $COOCH_3$); MPW, R_f 0.55 (pink); PW, R_f 0.87.

Anal. Calcd for $C_7H_{18}Cl_2N_2O_3$: C, 33.74; H, 7.28; Cl, 28.46; N, 11.25. Found: C, 33.86; H, 7.41; Cl, 28.66; N, 11.22.

Sodium Methoxide Treatment of Oxazoline (*cis* 15).—Pure oxazoline (*cis* **15**) (68 mg, 0.18 mmol) was dissolved in 10 ml of dry methanol, 1.0 ml of 0.88 *N* sodium methoxide was added, and the solution was allowed to stand for 20 min. Then 2.5 ml of water was added and the solution was refluxed for 30 min. When cooled, the solution was acidified to congo red with concentrated HCl and allowed to stand for 4 hr. The pH of the solution was adjusted to *ca.* 10 which after 10 min was reacidified with concentrated HCl and evaporated at 40° under vacuum until an oil began to form in the liquid. Methanol was added until the oil dissolved. Water was then added and the solution was scratched to induce crystallization. The product was collected by centrifugation and dried under vacuum at 46°: weight 62 mg (93%); mp 172–173° dec. The infrared spectrum was identical with that of *threo*-N,N′-dibenzoyl-β-hydroxylysine (*threo* **14a**), the starting material from which this oxazoline was prepared.

Direct Acid Hydrolysis of Oxazoline (*cis* 15).—The oxazoline (*cis* **15**) (83 mg, 0.23 mmol) was dissolved in 10 ml of methanol, 1.2 ml of 1 *N* HCl was added, and the solution was allowed to stand 18 hr to convert the oxazoline into the O-benzoyl compound. After the solution had been made basic with about 1.2 ml of *N* NaOH and had stood 10 min, enough base was added to bring the total volume of base to 3 ml and the solution was refluxed 30 min. The solution was then cooled to room temperature, acidified with concentrated HCl, and evaporated to an oily solid residue. After washing the residue twice with water, it was dissolved in 2 ml of methanol and diluted with 8 ml of water. This solution was then evaporated under vacuum to about 3 ml, after which a solid slowly crystallized from the solution. After centrifugation and drying at 46° under vacuum, 14 mg of *erythro*-N,N′-dibenzoyl-β-hydroxylysine (*erythro* **14a**) was collected, mp 159–162° dec. The infrared spectrum of this product was identical with *erythro* **14a**.

Registry No.—**6a,** 19991-86-7; **6b,** 19991-87-8; **8** hydrochloride, 19991-88-9; **10a,** 19991-89-0; **10b,** 19991-90-3; *erythro* **12a** hydrobromide, 19991-91-4; *threo* **12a** hydrobromide, 19991-92-5; *erythro* **12b** dihydrochloride, 19991-93-6; *threo* **12b** dihydrochloride, 19991-94-7; **13** hydrochloride, 19991-95-8; *erythro* **14a,** 19991-96-9; *threo* **14a,** 19991-97-0.

Synthetic Furocoumarins. IX. A New Synthetic Route to Psoralen[1]

LEONARD R. WORDEN,[2a] KURT D. KAUFMAN, JAMES A. WEIS, AND THOMAS K. SCHAAF[2b]

Department of Chemistry, Kalamazoo College, Kalamazoo, Michigan 49001

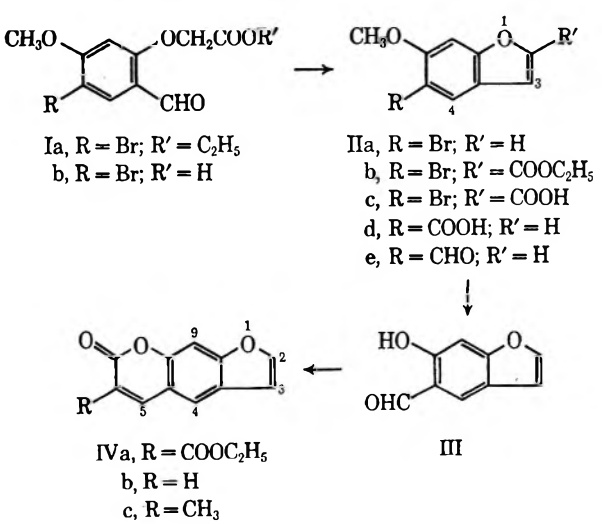
Received December 4, 1968

Practical syntheses of psoralen (IVb) and 3-methylpsoralen (IVc) from β-resorcylaldehyde are described. Bromination of ethyl (2-formyl-5-methoxyphenoxy)acetate gave the 4-bromo derivative Ia, which was saponified and simultaneously cyclized and decarboxylated to 5-bromo-6-methoxybenzofuran (IIa). Lithium–bromine interchange and then formylation and demethylation gave 5-formyl-6-hydroxybenzofuran (III), which was condensed with diethyl malonate to furnish psoralen after hydrolysis and decarboxylation of the Knoevenagel product IVa. Condensation of III with propionic anhydride furnished 3-methylpsoralen (IVc) directly.

Unfavorable directive effects associated with syntheses of psoralens unsubstituted in the 9 position have limited yields of the naturally occurring phototoxin psoralen (IVb, Scheme I) to 1–4% over-all from resorcinol or β-resorcylaldehyde.[3] However, Chatterjee and Sen recently reported a 15% conversion of resorcinol into psoralen.[4] Although their scheme now is the route of choice to psoralen itself, the synthesis lacks the versatility of the novel Scheme I, which represents a 14% conversion of β-resorcylaldehyde into psoralen.

Ethyl (4-bromo-2-formyl-5-methoxyphenoxy)acetate (Ia) was prepared both by bromination of ethyl (2-formyl-5-methoxyphenoxy)acetate[5] and by alkylation of 5-bromo-2-hydroxy-*p*-anisaldehyde.[6] Saponification of the ester Ia and then decarboxylative cyclization in acetic acid–acetic anhydride[7] gave the bromobenzofuran IIa and a trace quantity of a carboxylic acid identified as IIc by the independent synthesis of IIc from the ester Ia by base-catalyzed cyclization.

SCHEME I



To investigate the lithium–halogen interchange, the bromobenzofuran (IIa) was treated with butyllithium and then Dry Ice. This gave the carboxylic acid IId in quantitative yield. Earlier investigation of direct metalation with butyllithium of 6-methoxybenzofuran[8] and then carbonation (Dry Ice) indicated (thin layer chro-

(1) Part VIII: K. D. Kaufman, R. C. Kelly, and D. C. Eaton, *J. Org. Chem.*, **32**, 504 (1967). Preliminary communication: L. R. Worden and K. D. Kaufman, presented at the First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 1967.

(2) (a) To whom inquiries should be directed. (b) National Science Foundation Undergraduate Research Participant (Grant No. GE-4097).

(3) (a) E. Späth, B. L. Manjunath, M. Pailer, and H. S. Jois, *Ber.* **69**, 1087 (1936); (b) E. C. Horning and D. B. Reisner, *J. Amer. Chem. Soc.*, **70**, 3619 (1948); (c) R. T. Foster, A. Robertson, and A. Bushra, *J. Chem. Soc.*, 2254 (1948); (d) T. R. Seshadri and M. S. Sood, *Indian J. Chem.*, **1**, 291 (1963).

(4) D. K. Chatterjee and K. Sen, *Sci. Cult.* (Calcutta), **33**, 528 (1967).

(5) R. Andrisano, F. Duro, and G. Pappalardo, *Boll. Sci. Fac. Chim. Ind. Bologna*, **14**, 96 (1956).

(6) M. G. S. Rao, C. Srikantia, and M. S. Iyengar, *J. Chem. Soc.*, 1578 (1929); *Chem. Abstr.*, **23**, 4681 (1929).

(7) A. W. Burgstahler and L. R. Worden, *Org. Syn.*, **46**, 28 (1966).

(8) H. Dumont and St. v. Kostanecki, *Ber.*, **42**, 911 (1909).

matography) the formation of at least seven bicarbonate-soluble products.

Treatment of the bromobenzofuran (IIa) with butyllithium and then N-methylformanilide furnished the aldehyde IIe, which was demethylated to the key intermediate, 5-formyl-6-hydroxybenzofuran (III).[9] Condensation of this intermediate with diethyl malonate gave ethyl 3-psoralencarboxylate (IVa), which was hydrolyzed in glacial acetic acid–concentrated hydrochloric acid[10] and then decarboxylated with copper–bronze to psoralen (IVb). This sample was identical (melting point, mixture melting point, infrared and ultraviolet spectra) with an authentic sample of the natural product obtained from the Pharmaceutical Department of Sandoz Ltd., Basle, Switzerland, to whom we express our appreciation.

Perkin condensation of the aldehyde III with propionic anhydride furnished the new furocoumarin, 3-methylpsoralen (IVc).

Experimental Section[11]

Ethyl (4-Bromo-2-formyl-5-methoxyphenoxy)acetate (Ia). A. From Ethyl (2-Formyl-5-methoxyphenoxy)acetate.—Partial methylation of β-resorcylaldehyde with methyl iodide and K_2CO_3 in acetone furnished 2-hydroxy-*p*-anisaldehyde of mp 41.5–43° in 62% yield by steam distillation of the alkali-soluble portion of the organic residue obtained from the reaction (lit.[12] mp 41–42°).

Alkylation of 2-hydroxy-*p*-anisaldehyde with ethyl bromoacetate according to Andrisano and coworkers[5] furnished ethyl (2-formyl-5-methoxyphenoxy)acetate of mp 63–65.5° in quantitative yield (lit.[5] mp 68–69°, no yield stated). This material was sufficiently pure for use in the next step.

A stirred solution of 8.9 ml (0.17 mol) of bromine in 0.4 l. of glacial acetic acid was added at room temperature over a period of 15 min to a stirred solution of 39.0 g (0.164 mol) of ethyl (2-formyl-5-methoxyphenoxy)acetate in 0.2 l. of glacial acetic acid. The resulting solution was stirred for an additional 45 min and then diluted by the slow addition of 1.5 l. of ice water. The white, flocculent precipitate was stirred for 45 min, collected, and washed with water. The dried white powder weighed 49.8 g (96%) and was of sufficient purity for use in the next step, mp 117.5–120°.

The **semicarbazone** crystallized from a large volume of ethanol, mp 241.5–242.5°.

Anal. Calcd for $C_{13}H_{16}BrN_3O_5$: C, 41.72; H, 4.31; N, 11.23. Found: C, 41.90; H, 4.49; N, 10.99.

B. From 5-Bromo-2-hydroxy-*p*-anisaldehyde.—5-Bromo-2-hydroxy-*p*-anisaldehyde was prepared both by bromination of 2-hydroxy-*p*-anisaldehyde (see part A) according to Rao and coworkers[6] (73%) and by bromination of β-resorcylaldehyde according to Seshadri and Varadarajan[13] to give 5-bromo-β-resorcylaldehyde of mp 173–175.5° in 22% yield (lit.[13] mp 175–176°, no yield of pure material stated). Partial methylation with dimethyl sulfate then furnished 19% 5-bromo-2-hydroxy-*p*-anisaldehyde, mp 116–119° (lit.[13] mp 120–121°, no yield stated).

A mixture of 2.00 g (8.66 mmol) of 5-bromo-2-hydroxy-*p*-anisaldehyde, 1.2 ml (11 mmol) of ethyl bromoacetate, 15.6 g (11.3 mmol) of potassium carbonate, and 50 ml of acetone was stirred under reflux for 21 hr, then cooled and filtered. Evaporation of the acetone left a solid residue, which was leached thoroughly with ether. The ether was washed with cold 5% sodium hydroxide, dried, and evaporated to leave 1.81 g (66%) of a light yellow material which smelled strongly of ethyl bromoacetate. Crystallization from ligroin (bp 100–115°) and then carbon tetrachloride afforded 0.63 g (23%) of the ester Ia of mp 121.5–123.5°. An additional crystallization from carbon tetrachloride gave an analytical sample of long, white needles of mp 123.5–124.5°.

Anal. Calcd for $C_{12}H_{13}BrO_5$: C, 45.44; H, 4.13; Br, 25.20. Found: C, 45.40; H, 4.45; Br, 25.21.

(4-Bromo-2-formyl-5-methoxyphenoxy)acetic Acid (Ib).—A mixture of 49.5 g (0.156 mol) of the ethyl ester Ia, 500 ml of 95% ethanol, and 625 ml (0.625 mol) of 1 *N* aqueous sodium hydroxide was stirred under reflux for 1 hr, and then *ca.* 200 ml of solvent was removed by distillation. The resulting yellow solution was cooled to 0° and poured into a mixture of 200 ml of ice water and 53 ml (0.620 mol) of concentrated hydrochloric acid. The yellow precipitate was collected, washed with several portions of water, and dried to give 43.1 g (95%) of the acid Ib, mp (instantaneous) 218° dec. A small sample was recrystallized three times from glacial acetic acid for analysis, mp (instantaneous) 222° dec.

Anal. Calcd for $C_{10}H_9BrO_5$: C, 41.56; H, 3.14; Br, 27.66. Found: C, 41.67; 3.39; Br, 27.82.

5-Bromo-6-methoxybenzofuran (IIa).—A mixture of 5.00 g (0.0173 mol) of (4-bromo-2-formyl-5-methoxyphenoxy)acetic acid (Ib), 5.00 g (0.0609 mol) of powdered anhydrous sodium acetate, 125 ml of acetic anhydride, and 25 ml of glacial acetic acid was stirred under reflux for 2 hr and then poured onto 1 kg of cracked ice. Alternate portions of 20% aqueous sodium hydroxide and ice were added until the mixture was distinctly basic. The basic mixture was thoroughly extracted with ether, and the ether was washed with 5% aqueous sodium hydroxide, dried (brine and then $MgSO_4$), and evaporated to leave 3.40 g of a light brown oil that crystallized upon being cooled. The solid was chromatographed on 25 g of acid-washed alumina (eluted with 30–60° petroleum ether) to give 3.01 g (77%) of 5-bromo-6-methoxybenzofuran as light yellow crystals of mp 51–55°, which were sufficiently pure for use in the next step. Two crystallizations of a small sample from methanol gave white needles of mp 55–56°: ultraviolet λ_{max} (95% ethanol) 244 mμ (log ε 3.94), 252 (3.92), 292 (3.75), and 302 (3.68); nmr (CCl_4) τ 2.35 (s, 1, C_4-H), 2.56 (d, 1, J = 2 Hz, C_2-H), 3.05 (s, 1, C_7-H), 3.44 (d, 1, J = 2 Hz, C_3-H), and 6.13 (s, 3, CH_3).

Anal. Calcd for $C_9H_7BrO_2$: C, 47.60; H, 3.11; Br, 35.20. Found: C, 47.64; H, 3.25; Br, 35.50.

Acidification with concentrated hydrochloric acid of the aqueous layers from the ether extractions gave only trace amounts of 5-bromo-6-methoxy-2-benzofurancarboxylic acid (IIc).

Ethyl 5-Bromo-6-methoxy-2-benzofurancarboxylate (IIb) and 5-Bromo-6-methoxy-2-benzofurancarboxylic Acid (IIc).—A sodium ethoxide solution was prepared from 0.75 g (0.033 mol) of sodium and magnesium-dried[14] ethanol. To 5 ml of this solution was added 1.00 g (3.15 mmol) of the ester Ia and 10 ml of magnesium-dried ethanol. The solution was refluxed for 15 min and then cooled in an ice bath. A yellow precipitate which had formed during the course of the reaction dissolved when 25 ml of water was added cautiously to the reaction mixture, but a new light yellow crystalline precipitate appeared and was collected and dried, 0.20 g, mp 99–100°. Recrystallization from dilute ethanol gave 0.16 g (17%) of the ester IIb as off-white, slender needles of mp 100.5–101.5°.

Anal. Calcd for $C_{12}H_{11}BrO_4$: C, 48.18; H, 3.71; Br, 26.72. Found: C, 48.23; H, 3.76; Br, 26.34.

Acidification of the filtrate from which the 0.20-g precipitate had been collected gave 0.41 g of a mixture of 5-bromo-6-methoxy-2-benzofurancarboxylic acid (IIc) and (4-bromo-2-formyl-5-methoxyphenoxy)acetic acid (Ib). Fractional crystallization of the mixture from 95% ethanol gave 0.17 g (20%) of the benzofurancarboxylic acid IIc as a bright yellow, amorphous solid of instantaneous mp 284–285°. Sublimation followed by another crystallization from 95% ethanol gave a white solid of instantaneous mp 289.5–291.5°.

Anal. Calcd for $C_{10}H_7BrO_4$: C, 44.31; H, 2.60; Br, 29.48. Found: C, 44.42; H, 2.90; Br, 29.50.

(9) P. Karrer, A. Glattfelder, and Fr. Widmer [*Helv. Chim. Acta*, **3**, 541 (1920)] formylated 6-hydroxybenzofuran and obtained a material which they believed to be 5-formyl-6-hydroxybenzofuran, but which failed to yield psoralen when condensed with acetic anhydride. Robertson and coworkers[3c] later suggested that Karrer, *et al.*, had obtained the 2-formyl derivative. The synthesis described in this paper established unequivocally that the substance in question was not 5-formyl-6-hydroxybenzofuran since our material differs widely in chemical and physical properties from that reported by Karrer, Glattfelder, and Widmer.

(10) E. L. Eliel, M. T. Fisk, and T. Prosser, *Org. Syn.*, **36**, 3 (1956).

(11) Melting points (capillary) below 225° are corrected. Infrared, ultraviolet, and (in some cases) nuclear magnetic resonance spectra of most of the compounds described below are on file. Photocopies will be supplied on request.[2a] In nmr descriptions, s = singlet, d = doublet.

(12) E. Ott and E. Nauen, *Ber.*, **55**, 920 (1922). The authors prepared the same compound in 50% yield by partial alkylation with dimethyl sulfate.

(13) T. R. Seshadri and S. Varadarajan, *J. Sci. Ind. Res.*, **11B**, 39 (1952).

(14) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

6-Methoxy-5-benzofurancarboxylic Acid (IId).—To a solution of 0.500 g (2.20 mmol) of 5-bromo-6-methoxybenzofuran (IIa) in 10 ml of anhydrous ether was added 2.00 ml (2.32 mmol) of 1.16 *N* butyllithium[15] in ether. The reaction flask was stoppered and the reaction mixture, which became warm, was swirled for 2 min and then poured onto crushed Dry Ice. More ether was added, the solid carbon dioxide was allowed to evaporate, and the ether was extracted thoroughly with 5% sodium bicarbonate. The white solid recovered from the extract by acidification, extraction with ether, and removal of the ether was washed with three small portions of ether to remove adhering butyric acid: yield 0.42 g (99%); mp 140–141°. Crystallization of a small sample from dilute ethanol gave feathery needles of mp 144.5–145°.

Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.33; H, 4.11.

5-Formyl-6-methoxybenzofuran (IIe).—To a solution of 47.6 g (0.209 mol) of 5-bromo-6-methoxybenzofuran (IIa) in 0.8 l. of anhydrous ether was added rapidly 260 ml (0.21 mol) of 0.82 *N* butyllithium[15] in ether. The reaction mixture was stirred slowly for about 0.25 min and then added over a period of 5 min to a stirred solution of 55.5 g (0.411 mol) of redistilled N-methylformanilide in 0.5 l. of anhydrous ether. After being stirred for an additional 15 min, the ether solution was washed with water and then with 5% hydrochloric acid (four 200-ml portions). The ether was dried ($MgSO_4$) and evaporated to give a yellow oil which crystallized upon overnight refrigeration. Chromatography on 1.2 kg of silica gel (4-in.-diameter column, elution with 50% benzene in hexane) and then crystallization from cyclohexane afforded 25.45 g (69%) of 5-formyl-6-methoxybenzofuran as off-white crystals of mp 88.5–90°: nmr (CCl_4) τ −0.35 (s, 1, CHO), 2.03 (s, 1, C_4-H), 2.52 (d, 1, J = 2.5 Hz, C_2-H), 3.04 (s, 1, C_7-H), 3.32 (d, 1, J = 2.5 Hz, C_3-H), and 6.07 (s, 3, CH_3). Recrystallization of a small sample from ligroin (bp 60–90°) gave white needles of unchanged melting point.

Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.96; H, 4.61.

5-Formyl-6-hydroxybenzofuran (III).—Granular anhydrous aluminum chloride (3.05 g, 22.9 mmol, J. T. Baker Co. No. 0504) that had been powdered and then weighed rapidly in an open container on a dry day was added to 200 ml of freshly distilled, reagent grade 1,2-dichloroethane (Eastman Kodak Co., no. EK-132) in a flask protected with a drying tube. The straw-colored solution was warmed and stirred until *ca.* half the aluminum chloride had dissolved. Then 2.00 g (11.4 mmol) of 5-formyl-6-methoxybenzofuran (IIe) was added, and the resulting orange solution was heated under reflux for 1.25 hr. The mixture turned considerably darker during the course of the reflux period and slowly deposited a fine, brown precipitate after the first 0.5 hr. After the reflux period the reaction mixture was allowed to cool to room temperature and then was poured into a separatory funnel that contained 0.2 l. of 10% hydrochloric acid. Ether was added to bring the organic phase to the surface, the clear aqueous layer was discarded, and the ether solution was extracted repeatedly with 50-ml portions of 5% sodium hydroxide until the alkaline extracts remained colorless. The combined, cooled extracts were acidified, and the resulting flocculent tan precipitate was taken up in ether. The ether was dried ($MgSO_4$) and evaporated to give a tan residue, which was leached with 200 ml of boiling ligroin (bp 60–90°). The filtered ligroin solution was evaporated to dryness to leave 1.67 g (91%) of 5-formyl-6-hydroxybenzofuran as a pale yellow solid of mp 106.5–107.5°. Although this material was pure enough for use in the next step, a small sample was crystallized from ligroin (bp 60–90°) with activated carbon and then from 95% ethanol to give white needles of unchanged melting point.

(15) The reagent was prepared according to G. Wittig in "Newer Methods of Preparative Organic Chemistry," Vol. 1, Interscience Publishers, New York, N. Y., 1948, p 575, and standardized according to H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944). Butyllithium now is commercially available.

Anal. Calcd for $C_9H_6O_3$: C, 66.67; H, 3.73. Found: C, 66.89; H, 3.91.

The **semicarbazone** crystallized from 95% ethanol in lustrous, light yellow plates of instantaneous mp 283°. The melt resolidified immediately to a light orange solid.

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 55.02; H, 4.38; N, 19.11.

Ethyl 3-Psoralencarboxylate (IVa).—A mixture of 0.162 g (1.00 mmol) of 5-formyl-6-hydroxybenzofuran (III) and 2.0 ml of absolute ethanol was warmed to effect solution of the benzofuran, and then 0.18 ml (1.2 mmol) of diethyl malonate and 0.03 ml of piperidene were added with an accompanying red coloration. The reaction mixture was heated under reflux for 15 min and allowed to cool whereupon the product crystallized. Filtration furnished 0.216 g (84%) of orange plates, mp 151–152.5°. Two recrystallizations of a small portion from methanol for analysis gave long orange needles of mp 153–154°.

Anal. Calcd for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found: C, 65.04; H, 4.22.

Psoralen (IVb).—A mixture of 1.00 g (3.87 mmol) of ethyl 3-psoralencarboxylate (IVa), 7.5 ml of glacial acetic acid, and 3.5 ml of concentrated hydrochloric acid was heated under reflux for 2 hr and poured onto 25 g of crushed ice to furnish 0.87 g (98%) of the corresponding acid as a yellow powder of mp 258–261°. Two recrystallizations of a small sample from 1,2-dichloroethane gave yellow needles of mp 264.5–265.5° for which a satisfactory analysis was not obtained.

A mixture of 0.200 g (0.868 mmol) of crude 3-psoralencarboxylic acid, 0.500 g of copper–bronze powder (E. H. Sargent Co., No. SC-11552), and 3.0 ml of freshly distilled quinoline was heated under reflux for 10 min, allowed to cool, diluted wth 50 ml of ether, and then filtered to remove the copper–bronze. The ether solution was extracted repeatedly with 6 *N* hydrochloric acid until further extracts remained colorless. Evaporation of the dried ether layer gave a brown solid which upon sublimation at 145° (0.45 mm) and then recrystallization from dilute ethanol furnished 0.097 g (60%) of psoralen as long white needles of mp and mmp 165.5° (no range), infrared and ultraviolet spectra[16] identical with those of an authentic sample received from Sandoz Ltd.

3-Methylpsoralen (IVc).—A mixture of 0.486 g (3.0 mmol) of 5-formyl-6-hydroxybenzofuran (III), 0.572 g (6.0 mmol) of sodium propionate (Eastman Kodak practical grade), and 0.78 ml (6.1 mmol) of freshly distilled propionic anhydride was heated at 178–181° (oil-bath temperature) for 9 hr, cooled, and then stirred overnight with 15 ml of 3 *N* aqueous sodium acetate to decompose excess anhydride. The reaction mixture was worked up by ether extraction. Extraction of acidic materials with sodium bicarbonate solution and then drying and evaporation of the ether furnished a dark-colored solid which was sublimed at 170° (0.3 mm). Crystallization of the sublimate from ethanol furnished 0.279 g (47%) of 3-methylpsoralen as colorless needles of mp 235–235.5°. Recrystallization for analysis of a small sample from ethanol did not change the melting point.

Anal. Calcd for $C_{12}H_8O_3$: C, 71.99; H, 4.03. Found: C, 71.86; H, 4.38.

Registry No.—Ia, 20073-14-7; Ia semicarbazone, 20073-15-8; Ib, 20073-16-9; IIa, 20073-17-0; IIb, 20073-18-1; IIc, 20073-19-2; IId, 20073-20-5; IIe, 20073-21-6; III, 20073-22-7; III semicarbazone, 20073-23-8; IVa, 20073-24-9; IVb, 66-97-7; IVc, 20073-26-1.

Acknowledgment.—We thank the Upjohn Co., Kalamazoo, Mich., for determination of combustion data and nmr spectra.

(16) See D. K. Chatterjee, R. M. Chatterje, and K. Sen [*J. Org. Chem.*, **29**, 2467 (1964)] for a reproduction of the ultraviolet spectrum of psoralen.

Substituent Effects of Chlorine in Norbornanes[1]

ALBERT J. FRY AND WILLIAM B. FARNHAM

Chemistry Department, Wesleyan University, Middletown, Connecticut 06457

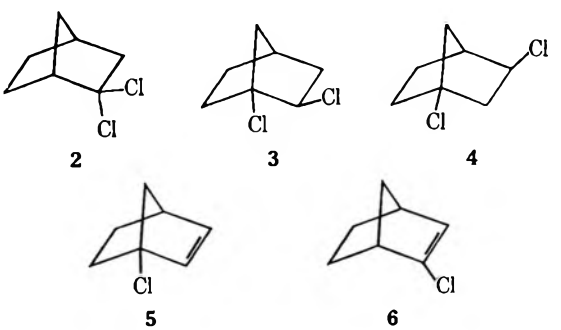
Received July 10, 1968

Hydrochlorinations of 1-chloronorbornene (**5**) and 2-chloronorbornene (**6**) afford 1,*exo*-3-dichloronorbornane (**4**) and 2,2-dichloronorbornane (**2**), respectively. Solvolytic and silver ion promoted ionization of **2**, **4**, and 1,*exo*-2-dichloronorbornane (**3**) have been examined. The results do not require the assumption of bridged intermediates. Hydroboration of **5**, followed by oxidation with alkaline hydrogen peroxide, results in a mixture of 1-chloro-*exo*-2-norbornanol (**11**, 38%) and 1-chloro-*exo*-3-norbornanol (**12**, 62%); this orientation differs from that observed in hydroboration of other allylic chlorides.

Much recent attention has been paid to the structure of the norbornyl cation and derivatives of it. In particular, debate has centered[2] on the question of whether the norbornyl cation is better represented as a σ-bridged ion, *i.e.*, a resonance hybrid of structures **1a** and **1b**, or as a rapidly equilibrating mixture of classical

1a **1b**

ions **1a** and **1b**. Saunders, Schleyer, and Olah have presented nmr evidence[3] that the parent norbornyl ion maintains symmetry down to $-120°$ in SbF_5–liquid SO_2, a result more compatible[2a] with a single species. On the other hand, no evidence compels the formulation of 2-phenyl-2-norbornyl[4] or even 2-methyl-2-norbornyl[5] cations as anything but classical. The norbornyl system is in fact constituted of a mixture of electronic and steric[2c] effects, readily perturbed by substituents.[6] For this reason, it is not clear whether data obtained with substituted norbornyl cations (except for substitution by deuterium[6a]) may be used with certainty as a diagnostic for structure of the parent ion. It is more appropriate to ask what evidence there is, for a given substituent, X, requiring formulation of X-substituted norbornyl cations, or better, the transition states leading to them,[7] as either classical or bridged. In this context and in view of the fact that previous studies of substituted norbornyl cations have not involved strongly electronegative substituents, we have studied the effect of substitution by chlorine upon several cationic reactions in the norbornyl series. Included were both solvolytic and silver ion promoted ionization of 2,2-dichloronorbornane (**2**), 1,*exo*-2-dichloronorbornane (**3**), and 1,*exo*-3-dichloronorbornane (**4**), the hydrochlorination of 1-chloro- and 2-chloronorbornenes (**5** and **6**, respectively), and the orientation in hydroboration of 1-chloronorbornene **5**. Hydroboration, although sensitive to electronic effects, does not involve carbonium ions;[8] it demonstrates the response of the system to inductive electron demand and was also used in structural correlations.



2 **3** **4**

5 **6**

Synthesis and Reactions of 1-Chloro- and 2-Chloronorbornenes.—Wilt and coworkers[9] have reported the slow rearrangement of **2** to an apparent equilibrium mixture consisting of 20% **2**, 64% **3**, and 16% 1,*endo*-2-dichloronorbornane (**7**) under the action of a slurry of aluminum chloride in carbon tetrachloride. It is not clear from the experimental data whether in fact a true equilibrium was obtained, since irreversible tar-forming reactions were taking place and no attempt was made to approach the equilibrium from **3** or **7**. We had independently observed the Lewis acid promoted isomerization of **2**. Under our conditions rearrangement takes a somewhat different course. When **2** is added to a *homogeneous solution* of aluminum chloride in dichloromethane,[10] a pale yellow solution is obtained. Work-up and analysis by vpc after 30 min shows both the *absence* of **2** and the presence of **3** and **7**, in 3:1 ratio; when the reaction time is extended to 24 hr, the mixture is much darker and the ratio of **3** to **7** is close to 1:1. Isomerization of **2** in toluene by the weaker Lewis acid, stannic chloride, is considerably slower than the aluminum chloride reaction, but is more specific, and is the synthetic method of choice for **3**. The only volatile product is **3**, and the conversion of **2** into **3** is conveniently monitored by vpc. We have been interested in this isomerization as a synthetic route to **3** but it is clear that product composition in the isomerate is quite dependent upon experimental conditions. These experiments suggest **3** as the initial

(1) A portion of this research has been reported in preliminary form: A. J. Fry and W. B. Farnham, *Tetrahedron Lett.*, 3345 (1968).

(2) (a) P. D. Bartlett, "Non-Classical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965; (b) H. C. Brown and C. J. Kim, *J. Amer. Chem. Soc.*, **90**, 2082 (1968); (c) P. von R. Schleyer, *ibid.*, **89**, 701 (1967).

(3) (a) M. Saunders, P. von R. Schleyer, and G. A. Olah, *ibid.*, **86**, 5680 (1964); (b) G. A. Olah, A. Commeyras, and C. Y. Lui, *ibid.*, **90**, 3882 (1968).

(4) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *ibid.*, **86**, 1246, 1247, 1248 (1964).

(5) H. C. Brown and M.-G. Rei, *ibid.*, **86**, 5004 (1964).

(6) (a) J. P. Schaefer, M. J. Dagani, and D. S. Weinberg, *ibid.*, **89**, 6938 (1967); (b) J. F. Chiang, C. F. Wilcox, Jr., and S. H. Bauer, *ibid.*, **90**, 3149 (1968). The latter paper describes significant differences in geometry between norbornane and 1,4-dichloronorbornane. The ability of the system to accommodate bridging ought to be a sensitive function of changes in geometry.[2]

(7) *Cf.* B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms—1965," John Wiley & Sons, Inc., New York, N. Y., 1966, Chapter 1.

(8) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(9) J. W. Wilt, C. T. Parsons, C. A. Schneider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.*, **33**, 694 (1968). We thank Professor Wilt for a preprint of his work.

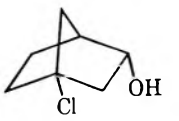
(10) G. Baddeley, *Quart Rev.* (London), **8**, 355 (1954).

kinetically controlled product, and **7** as the product of subsequent isomerization. Solvolytic data on **2** and **3** (*vide infra*) support this belief: **2** ionizes far more easily than **3**, and **7** is undoubtedly even less reactive than **3**.[2]

Alkenes **5** and **6**[11] were readily available through dehydrohalogenation of **3** and **2**, respectively, under the action of potassium *t*-butoxide in dimethyl sulfoxide.

A recently described technique[12] for hydrochlorination was used, and, as others have reported,[13] low temperatures were necessary for rapid addition. Hydrochlorination (CCl_4, −78°) of **6** yields **2** quantitatively in less than 10 min; under the same conditions norbornene (**8**) is also converted rapidly and quantitatively into *exo*-norbornyl chloride (**9**), containing a trace (<1% by vpc analysis) of *endo*-norbornyl chloride.[14] 1-Chloronorbornene, however, when subjected to these conditions, is recovered unchanged after an 8-hr interval. This unreactivity is confirmed by competitive experiments. Hydrochlorination (CCl_4, −78°) of 50:50 mixtures of **5** and **6**, **5** and **8**, or **6** and **8** results in rapid quantitative addition of hydrogen chloride to **6** and **8** without any measurable reaction of **5**. However, use of methylene chloride as solvent did result in slow hydrochlorination of **5** (~90% reaction after 10 hr in a preparative run).[15] The major product is 1,*exo*-3-dichloronorbornane (**4**). This constituted somewhat more than 99.5% of the product by vpc analysis; only one other product (<0.5%), with the same retention time as **2**, was observed. Since this was formed in amounts too small to isolate, the possibility remains that it is the as yet unknown 1,*endo*-3-dichloronorbornane (this possibility was not pointed out in ref 1). Although 0.1% of **3** could have been detected, none was found. The *exo* attachment of chlorine in the major product was assigned on the basis of several reports of almost exclusive attachment of chlorine in hydrochlorination of norbornenes.[2c,16,17] Further structural evidence supporting structure **4** was obtained through dehydrohalogenation to **5**, and by silver nitrate assisted hydrolysis of **4** (*vide infra*) to 1-chloro-3-*endo*-norbornanol (**10**). The alcohol **10** was subsequently oxidized to 1-chloro-3-norbornanone (**14**).[18]

7 **8** **9**



10

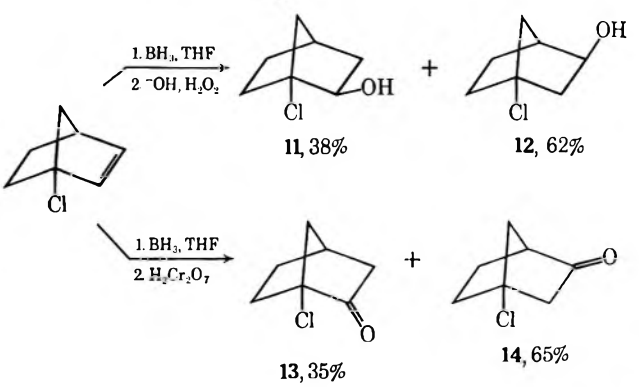
We have previously presented arguments[1] that the observed orientation in hydrochlorination of **5** is evidence against σ bridging in the transition state for hydrochlorination.

In brief, it was suggested that a bridged transition state would afford a mixture predominating in **2** and **3**, while the unbridged transition state would afford **4**. The Hammond postulate[19] was applied to suggest that the first *intermediate* in the hydrochlorination is likewise not bridged, but, since the relative energies of reactants and intermediate is not known, this postulate cannot be invoked here. Our data (*e.g.*, the orientation in addition to **6**) suggest that the transition states are cationic but do not allow statements about further stages along the reaction coordinate.

The unreactivity of **5** in hydrochlorination is worth further comment. We have found that allyl and crotyl chlorides and 1-chloro-1-butene are not hydrochlorinated measurably in 8 hr under conditions (CH_2Cl_2, −78°) where **5** (slowly) and **6** (rapidly) add hydrogen chloride. The markedly higher reactivity of both norbornenes relative to the acyclic alkenes is undoubtedly due to the strain in this ring system.[20] The slower rate of hydrochlorination of the haloalkenes is probably due to inductive electron withdrawal by halogen enhanced by hydrogen bonding of the halogen atom to hydrogen chloride.[21,22]

Whereas protonation of **5** in hydrochlorination occurs at the 2 position with >99.5% specificity, attachment of boron in hydroboration is slightly favored at the **3** position (Scheme I). It is reported that hydroborations of crotyl chloride[23] and 3-chlorocyclohexene[24] result in essentially complete addition of the boron

SCHEME I



(11) N. A. LeBel, P. D. Beirne, E. R. Karger, J. C. Powers, and P. M. Subramanian, *J. Amer. Chem. Soc.*, **86**, 3199 (1963).

(12) H. C. Brown and M.-H. Rei, *J. Org. Chem.*, **31**, 1090 (1966).

(13) (a) L. Schmerling, *J. Amer. Chem. Soc.*, **68**, 195 (1946); (b) H. Kwart and J. L. Nyce, *ibid.*, **86**, 2601 (1964).

(14) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *ibid.*, **88**, 4922 (1966).

(15) The function of methylene chloride in assisting hydrochlorination[12] is not clear; it has a lower melting point and higher dielectric constant than carbon tetrachloride, and also dissolves rather large amounts of hydrogen chloride at −78°. Any or all of these might contribute.

(16) (a) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 3901 (1967); (b) H. C. Brown and K. T. Lin, *ibid.*, **89**, 3898, 3900 (1967); (c) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *ibid.*, **88**, 4922 (1966).

(17) Professor Boris Franzus has carried out spin-decoupling nmr experiments on **4** which indicate that the proton at C-3 (>CHCl) is coupled not only to the vicinal protons at C-2 but to a third proton. The magnitude of this last coupling constant (J = 1.8–2.1 cps) is more consistent with H_{endo}–H_{anti} long-range coupling than with H_{exo}–$H_{bridgehead}$ coupling, which is usually larger (3–4.3 cps). Dr. Franzus will report the spectral details, which also indicate some skeletal distortion in **4**, in a forthcoming manuscript.

(18) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Amer. Chem. Soc.*, **83**, 3998 (1961).

(19) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(20) T. Beier, H. G. Hanthal, and W. Pritzkow, *J. Prakt. Chem.*, [4] **26**, 304 (1964).

(21) A. J. Fry, *Tetrahedron Lett.*, 5853 (1968).

(22) R. West, D. L. Powell, L. S. Whatley, M. K. T. Lee, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **84**, 3221 (1962).

(23) H. C. Brown and R. M. Gallivan, Jr., *ibid.*, **90**, 2906 (1968).

(24) P. Binger and R. Koster, *Tetrahedron Lett.*, 156 (1961).

atom to the position β to chlorine, followed by elimination and rehydroboration.

This directive effect of chlorine was thought to be inductive.[23] However, our results suggest that the directive effect of chlorine must be more complex, since otherwise **11** and **13** would have been the exclusive products of hydroboration. It may be that coordination of the chlorine atom to the incoming hydroborating agent plays a role in the previously observed specific β orientations.[23,24] The ratio of **11** to **12** is similar to that obtained in the hydroboration of 5-*exo*-methoxynorbornene.[25] (Because of the hygroscopic nature of **11**–**13**, these are presumed structures, based on nmr and ir data; see the Experimental Section.)

The structural assignments for products **11**–**14** rest upon the fact that the ratios of **11**:**12** and **13**:**14** are the same within experimental error, as is reasonable, since the hydroboration step controls orientation and is the same for both. Since the major ketone is **14** (see the ir and nmr spectral data in the Experimental Section), the major alcohol must be **12**. The *exo* configuration in **11** and **12** is assigned by analogy to the hydroboration of other norbornenes.[8,25] The general shape of the >CHOH proton in the two alcohols supports this assignment.[26]

Silver Ion Assisted Hydrolyses.—Chlorides **3**, **4**, and **9** were suspended in aqueous silver nitrate at steam-bath temperatures until starting material, as monitored by vpc, had disappeared. The qualitative order of reaction was **9** > **4** > **3**; under these conditions, only **3** was incompletely reacted after 8 hr. The only product isolated from **3** was norcamphor. From **9** there were isolated *exo*-norbornanol (identical with synthetic material[8]) and a nitrate ester of unknown configuration, in the ratio of 3:1. From **4** there were again isolated both an alcohol and a nitrate, in ratio of 2:1. The alcohol must be 1-chloro-3-*endo*-hydroxynorbornane (**10**) from the fact that it may be oxidized to 4-chloronorcamphor **14** and the observation that the low-field proton (>CHOH) in its nmr spectrum appears at τ 6.15, while that in its epimer **12** appears at τ 6.55. Many studies have shown that *exo* protons occur at lower field than do *endo* protons for epimers in the norbornane series.[27]

The fact that the silver ion assisted hydrolysis of **4** proceeds with inversion of configuration, while the corresponding reaction with *exo*-norbornyl chloride **9** proceeds with retention of configuration (based on the observed geometry of the alcohols isolated) is consistent with a previously suggested mechanism involving gradations of SN1 and SN2 behavior for reactions of silver ion with alkyl halides.[28] For *exo*-norbornyl chloride, ionization should be much preferred[29] over SN2 displacement by water or nitrate; this would result in over-all retention of configuration, as is observed. On the other hand, 1,3-dichloride **4** ionizes much less easily than **9** (see the next section on solvolytic experiments); apparently ionization is so unfavorable that carbon–chlorine bond breaking must require nucleophilic assistance by the solvent, this process resulting in inversion of configuration. Kornblum and Hardies[28] have also noted that, for reactions of alkyl halides with silver salts, inversion increases with decreased ionizing propensity of the halide.

The very slow reaction of **3** with silver nitrate deserves comment. In view of the fact that chlorine can stabilize a positive charge on the carbon to which it is attached[30] (*cf.* the hydrochlorination of 2-chloronorbornene and, in the next section, ease of ionization of 2,2-dichloronorbornane), the chlorine atom at the bridgehead in **3** should stabilize any positive charge appearing at C-1 during ionization. The low rate of reaction with silver ion suggests that bridging cannot be far advanced in the transition state for reaction of **3** with silver ion, if indeed it is involved at all.

Solvolytic Studies on Dichloronorbornanes.—Since a number of chloro-substituted *exo*-norbornyl chlorides were in hand, it was of interest to examine solvolytic routes to the corresponding chloronorbornyl cations. In order to make comparisons with rate data in the literature,[16a] kinetic measurements were made at 70.0° in 80% ethanol. For reasons to be described below, it was preferable to add a slight excess of sodium acetate and to titrate for chloride liberated. Because of the surprisingly slow solvolysis of **3** and **4**, only estimates of their reactivity could be obtained.

1. 2,2-Dichloronorbornane (**2**).—The solvolytic behavior of this substance was investigated in greatest detail. The products of solvolysis in 80% ethanol are 2-chloronorbornene **6** and norcamphor (**15**). When no sodium acetate was used, and the reaction rate was followed by titration of liberated acid with 0.020 *N* NaOH, a first-order plot was not obtained. It was then found that **6** is slowly converted into norcamphor in the presence of acid in 80% ethanol. An attempt was made to see if the hydrogen chloride catalyzed hydrolysis of **6** fit an autocatalytic kinetic expression,[31] but no simple rate law fit the data: an infinity titer was never obtained, and the amount of acid present actually began to decrease after 500 hr. Cristol and Caple[32] have likewise noted slow consumption of hydrogen chloride by ethanol solutions, presumably as a result of ethyl chloride formation.[33] Because of the complications in making kinetic measurements in the presence of acid, a small excess of sodium acetate was added, and a good first-order plot was obtained, in a manner to be shown below. The percentage of **6** in the products (**6** and **15**) remained constant at 56 ± 1% (by vpc) throughout the solvolysis. It is clear that **6** is not formed *via* an E2 reaction involving **2** and sodium acetate, for the following reasons. First, **6** is present in the same proportion in the early stages of solvolysis carried out in the absence of sodium acetate, and, second, the sodium acetate was not present in high enough initial concentration to yield a pseudo-first-order kinetic expression.

(25) P. J. Stang and P. von R. Schleyer, paper P-192 presented at the 155th National Meeting of the American Chemical Society, April 1968. We thank Professor Schleyer for a manuscript describing his work.

(26) W. C. Baird, Jr., *J. Org. Chem.*, **31**, 2411 (1966), and references therein.

(27) *E.g.*, T. J. Flautt and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 3212 (1963).

(28) N. Kornblum and D. E. Hardies, *ibid.*, **88**, 1707 (1966).

(29) Schaefer, *et al.*, have commented on the difficulty in forcing the SN2 pathway on *exo*-substituted norbornanes, even in nonpolar solvents.[6a]

(30) N. C. Deno, G. W. Holland, Jr., and T. Schulze, *J. Org. Chem.*, **32**, 1496 (1967).

(31) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961.

(32) S. J. Cristol and R. Caple, *J. Org. Chem.*, **31**, 2741 (1966).

(33) Under neutral conditions olefin **6** reacts less than 1% (vpc analysis) in 560 hr.

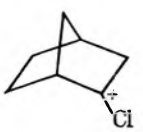
Formation of **6** from **2** requires liberation of one chloride ion, while formation of norcamphor results in liberation of two chloride ions per mole of **2** reacted. Since the reaction is followed by titration of chloride generated, a modification of the usual first-order kinetic expression must be used. It may be shown that, if **2** is disappearing by a first-order process, expressions 1 and 2 should hold, where a is the initial concentration of

$$\ln (a - by) = kt \quad (1)$$

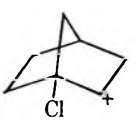
$$b = \frac{100}{(\%\ 6)(1) + (\%\ 15)(2)} \quad (2)$$

dichloride, y is the concentration of chloride ion at time t, and $1/b$ is the number of moles of chloride ion formed per mole of **2** reacted. From the measured product ratio, and also from an infinity titration, $b = 0.69$, and in fact, only for this value of b is the plot of the titration data a straight line. The value calculated is $k = (2.47 \pm 0.04) \times 10^{-5}$ sec^{-1} (Figure 1). Dichloride **2**, therefore, solvolyses 5.5 times faster than *exo*-norbornyl chloride **9** [$k = (4.47 \pm 0.04) \times 10^{-6}$ sec^{-1}].[16a]

The increased rate of solvolysis of **2** over **9**, formation of **6** and **15** as products, and the constant ratio of **6**:**15** thoughout the reaction are most economically interpreted in terms of rate-determining ionization of **2** to the α-chlorocarbonium ion **16**, which would then



16



17

partition itself between proton loss to afford **6** and reaction with solvent to yield, ultimately, norcamphor. Queen and Robertson[34] have concluded, from measurements of heat of activation and from deuterium kinetic isotope effects, that several 2,2-dihalopropanes solvolyze in water by the SN1 mechanism, and Streitweiser[35] has interpreted the net accelerating effect of an α-chloro substituent on the rates of ionization of alkyl halides as a resultant of inductive electron withdrawal and electron release by the resonance effect. The synthesis of deuterium-substituted analogs of **2** is in progress, in order to gain further information on the detailed course of solvolysis.

2. 1,*exo*-2-Dichloronorbornane (3) and 1,*exo*-3-Dichloronorbornane (4).—When 1,*exo*-2-dichloronorbornane (**3**) was heated in 80% ethanol at 85° for 480 hr no norcamphor or other product could be detected by vpc. Assuming that 0.5% product could have been detected (control experiments corroborated this), it may be concluded that less than 0.5% reaction occurred. At 70.0°, less than 0.2% reaction (by titration) occurred in 795 hr. The *upper limits* for the first-order rate constants for solvolysis of **3** based on these data are 7×10^{-10} sec^{-1} at 70° and 2.8×10^{-9} sec^{-1} at 85°. *exo*-Norbornyl chloride **9** solvolyzes, therefore, faster than **3** by a factor of at least 6.4×10^3 at 70° and 7×10^3 at 85.[16a] These rate constants correspond to half-lives at 70° for **9** and **3** of 42 hr and >30 yr.

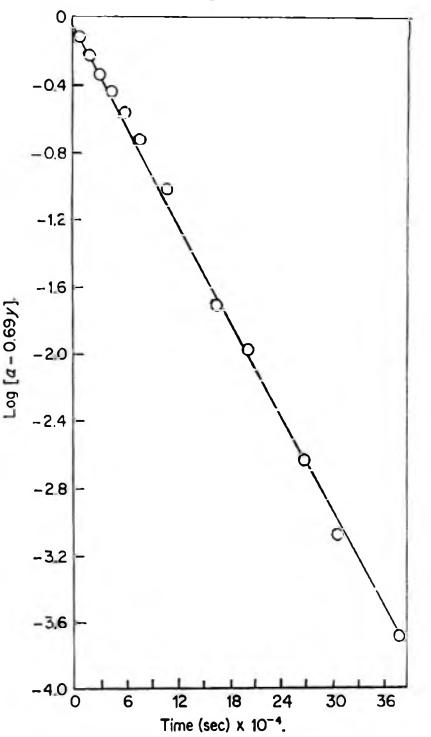


Figure 1.—Plot of the logarithm of the concentration of 2,2-dichloronorbornane *vs.* time in 80% ethanol at 70.0°, $a = 0.171$ *M*.

Although solvolysis of 1,*exo*-3-dichloronorbornane (**4**) does proceed, as evidenced by titration and vpc analysis, it is also very slow; it was followed to only 5% reaction, which took 530 hr. A very rough approximation of the first-order rate constant was made with $k = 2.7 \times 10^{-8}$ sec^{-1}. Because of experimental error in determination of chloride ion and the fact that only 5% of the starting material had reacted, the only significant part of the rate constant is the order of magnitude 10^{-8}. Norbornyl chloride ($k = 4.47 \times 10^{-6}$ sec^{-1}), therefore, ionizes faster than **4** by a factor of $(2 \pm 1) \times 10^2$.

In order to assess the effect of the bridgehead chlorine in **3** upon its rate of ionization, one might imagine two extremes for the ionization transition state. If it were unbridged (**17**) the only effect of chlorine would be inductively destabilizing. If, on the other hand, bridging were far advanced, then the resonance effect would allow stabilization and hence rate acceleration. The actual situation could be anywhere between these two extremes, but, to the extent that bridging is important, the rate of ionization of **3** should be larger than that expected on purely inductive grounds. The low observed rate demonstrates that bridging, at the least, cannot be far advanced in the transition state for ionization. There remains the question whether there is any contribution at all from bridging in the transition state. The minimum value of 7×10^3 for the ratio of solvolysis rates of **9** and **2** may be compared to the observation that *t*-butyl chloride solvolyzes 4×10^3 times faster than 1,2-dichloro-2-methylpropane (**18**) in 80% ethanol at 79°,[36] suggesting the naive interpretation that we are observing the extreme case of ionization without bridging. In fact, however, this conclusion is

(34) A. Queen and R. E. Robertson, *J. Amer. Chem. Soc.*, **88**, 1363 (1966).
(35) A. Streitweiser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 102.
(36) See ref 35, p 124. The rate depression upon substitution by chlorine is quite close to that predicted by a Taft treatment, suggesting that chlorine does not participate in the solvolysis of **18**.

not warranted, for the 1,3-dichloride **4** solvolyzes substantially more slowly than one would expect using a Taft treatment[37] with commonly observed values for σ^* and ρ^*, and the attenuation of the inductive effect through an extra bond. Since the norbornyl system may therefore be unusually sensitive to inductive effects, we cannot predict the rate of ionization expected for **3** on purely inductive grounds. We can say that these data at present do not require assumption of bridging in ionization of **3**. Clearly there is a need for much more data concerning the response of the norbornyl system to inductive effects of substituents, particularly those which are strongly electronegative.

Experimental Section[38]

2,2-Dichloronorbornane (**2**) was prepared by the method of Bixler and Niemann.[39] The product was >99.8% pure (trace of **6**) by vpc (Zonyl E-7, 120°, and SE-30, 125°). It was purified by preparative vpc for kinetic experiments. The nmr spectrum consists of two multiplets from τ 7.0 to 7.3 and from 8.0 to 9.0 (relative areas 1:4, respectively).

1,*exo*-2-Dichloronorbornane (**3**).—Stannic chloride, 6.5 g (25 mmol), was added to a solution of 20.0 g (122 mmol) of **2** in 100 ml of toluene, and the mixture stirred at 55° for 30 hr, after which time vpc (Zonyl E-7, 120°) showed the absence of **2**. Following the addition of 100 ml of pentane, the mixture was washed with 100 ml of cold 25% sulfuric acid and two 150-ml portions of water. A small amount of black insoluble material was filtered, the organic extracts were dried over magnesium sulfate, and the solvents were distilled through a glass helix packed column. Distillation afforded 15.6 (78%) of **3**: bp 103.5–105° (26–28 mm); mp 32–33° [lit.[9] bp 77° (11 mm)]; homogeneous by vpc (Zonyl E-7, 110°).

1-Chloronorbornene (**5**).—To a solution of 11.2 g (68 mmol) of **3** in 60 ml of dimethyl sulfoxide was added 11.0 g (98 mmole) of potassium *t*-butoxide. The mixture was stirred magnetically for 24 hr at room temperature. After dilution with 250 ml of water, the mixture was extracted with 200 ml of pentane. The aqueous phase was diluted with 100 ml of water and extracted twice with 150-ml portions of pentane. The combined pentane extracts were washed three times with water and dried over magnesium sulfate. Pentane was separated by distillation through a glass helix packed column. Distillation afforded 6.0 g (69%) of **5**: bp 86–88° (130 mm) [lit.[9] 75.5–77.5° (95 mm), 68%]. This material was homogeneous by vpc (Carbowax 20M, 95° and SE-30, 110°).

Hydrochlorination of 6.—A procedure described previously[12] was used, except that instead of the glass-tipped buret and valve of the analytical unit, the valve of the preparative unit was used. Contact of the concentrated hydrochloric acid with metal was avoided by connecting a glass-tipped syringe with the mercury in the valve by a flexible Teflon needle (Hamilton Co.) piercing the rubber septum of the valve. The apparatus was flushed with hydrogen chloride and chilled to −78°. A solution of 0.40 g of **6** and 1 ml of carbon tetrachloride was added; uptake of hydrogen chloride began immediately and had ceased after 10 min. Vpc (Zonyl E-7, 115°) indicated complete conversion into **2**; the same result was obtained using dichloromethane as solvent.

Competitive Hydrochlorination Experiments.—An equimolar mixture of **5** and **6** in carbon tetrachloride was treated as previously described. Examination by vpc after 10 min showed only **5**, **2**, and a trace of **7**. Similar treatment of a mixture of **5** and **8** showed the presence of only **5** and *exo*-norbornyl chloride (**9**). An equimolar mixture of **6** and **8** was converted completely into **2** and **9** under these conditions.

1,*exo*-3-Dichloronorbornane.—A solution of 4.5 g of **5** in 10 ml of dichloromethane was allowed to react according to the above procedure. After 10 hr at −78°, the mixture was washed with 20 ml of water and dried over magnesium sulfate. After distillation of the solvent and a small amount of unreacted **5**, vpc analysis (Zonyl E-7, 130°) indicated only two components, 1,*exo*-3-dichloronorbornane **4** (>99.5%) and a peak with the same retention time as **2**. The nmr spectrum of **4** consists of two multiplets, at τ 6 and between 7.3 and 8.8 (relative areas 1:9); the ir spectrum of **4** differs considerably from those of **2** and **3** between 8.0 and 11.6 μ; the strongest peaks appeared at 8.38, 8.58, 9.48, 9.88, 10.15, 10.50, 10.88, 11.00, and 11.56 μ.

Anal. Calcd for $C_7H_{10}Cl_2$: C, 50.93; H, 6.11; Cl, 42.96. Found: C, 50.99; H, 6.07; Cl, 43.18.

Hydroboration–Chromic Acid Oxidation of 5.—To a solution of 1.0 g of **5** in 1 ml of tetrahydrofuran at 0° was added, through a rubber septum, 3.5 ml of a 1.0 *M* solution of diborane in tetrahydrofuran (Metal Hydrides, Inc.). After 15 min, 0.5 ml of water was added, followed by dropwise addition of a solution of 1.72 g of sodium dichromate dihydrate and 1.30 ml of concentrated sulfuric acid in 7 ml of water. After 1.5 hr, 10 ml of water was added, and the mixture was extracted with ether. The ether extracts were washed three times with water and dried over magnesium sulfate; the solvent was then removed at the rotary evaporator. Vpc (SE-30, 135°) showed two products in 65:35 ratio. Theses were separated by preparative vpc and possessed distinctly different spectral properties. The major ketone, 1-chloro-3-norbornanone, **14**, had three multiplets in its nmr spectrum at τ 7.6, 7.9, and 8.3 (relative areas 1:2:6) and characteristic ir bands at 7.78, 8.15, 8.21, 8.54, 8.65, 9.38, 9.92, 10.10, 10.48, and 10.60 μ; these properties are identical with those reported for **14**,[18] except that the carbonyl appears at 5.70 rather than 5.73 μ. The minor ketone, 1-chloro-2-norbornanone, **13**, had the following characteristics: nmr, two multiplets at τ 7.3 and from 7.6 to 8.5 (relative areas 1:8.5); ir 5.65 (C=O), 7.70, 8.48, 9.21, 9.75, 10.44, and 11.47 μ.

Hydroboration–Alkaline Hydrogen Peroxide Oxidation of 5.—To a solution of 2.3 g of 5 in 4.6 ml of tetrahydrofuran was added 4.6 ml of a 1 *M* solution of diborane in tetrahydrofuran. After 15 min, there were added 1.9 ml of 3 *M* sodium hydroxide and 1.4 ml of 50% hydrogen peroxide. The products were isolated as in the preceding reaction. Vpc (SE-30, 135°) showed two solid products in the ratio of 62:38. These were separated by preparative vpc. The nmr spectrum of the minor isomer 1-chloro-2-*exo*-norbornanol, **11**, mp 75.5–77.5°, consists of a multiplet at τ 6.3, singlet at 7.05, and multiplet from 7.7 to 9.0 (relative areas 1:1:9); the nmr spectrum of the major alcohol 1-chloro-3-*exo*-norbornanol, **12**, mp 86–87°, consists of a multiplet centered at τ 6.55, singlet at 7.3, and multiplet from 7.75 to 9.0 (relative areas 1:1:9, respectively). The singlets at τ 7.05 and 7.3 in the two spectra are concentration dependent and are assigned to hydroxyl protons in the two alcohols. Microanalytical data were unsatisfactory, since the two alcohols were hygroscopic.

Silver Nitrate Assisted Hydrolysis of 4.—To a solution of 0.125 g (0.73 mmol) of silver nitrate in 0.3 ml of water was added 0.10 g (0.61 mmol) of **4**. The flask was stopped and heated on the steam bath with frequent vigorous stirring. After 3 hr, vpc analysis indicated that **4** had completely reacted. After cooling and extraction with ether, the ether extracts were washed with water and dried over magnesium sulfate, and the solvent was removed at the rotary evaporator. Vpc analysis (SE-30, 130°) showed two products in ~2:1 ratio. The minor isomer had an nmr spectrum consisting of a multiplet at τ 5.1 and another multiplet from 7.35 and 8.70 (relative areas 1:9.6); the strongest peak in the ir spectrum appears at 6.1 μ ($-ONO_2$). The major product, 1-chloro-3-*endo*-norbornanol (**10**), had ir absorption at 2.78, 3.00, and 9.00 μ (>CHOH); its nmr spectrum consisted of a multiplet at τ 6.15 (>CHOH), concentration-dependent singlet at ~6.5 (OH), and a multiplet from 7.55 to 8.75 (relative areas 1:1:9.3). The vpc retention time of **10** was clearly different from that of **12**.

Silver Nitrate Assisted Hydrolysis of 9.—*exo*-Norbornyl chloride (prepared by hydrochlorination of **8**) was treated with aqueous silver nitrate as above. Vpc analysis (SE-30, 125°) showed two products, in the ratio of 3:1. The major product

(37) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, Chapter 13.

(38) Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Nuclear magnetic resonance spectra were recorded in carbon tetrachloride on a Varian A-60A spectrometer, relative to external tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 137 infrared spectrophotometer. A Varian Aerograph Model 90-P gas chromatograph was used for preparative and analytical separations. Three columns were used: a 2 ft × 0.25 in. column packed with 15% Zonyl E-7 on 20/40 mesh Fluoropak 80; a 5 ft × 0.25 in. column packed with 20% SE-30 on 60/80 mesh Chromosorb W; and an 18 in. × 0.25 in. column packed with 15% Carbowax 20M on 20/40 mesh Fluoropak 80. Column temperatures are reported for individual experiments.

(39) R. L. Bixler and C. Niemann, *J. Org. Chem.*, **23**, 742 (1958).

was identical with a sample of *exo*-norbornanol prepared by hydroboration of norbornene.[8] The low-field proton (<CHOH) in the nmr spectrum of each alcohol appeared at τ 6.38. The minor isomer was a nitrate, ir 6.1 μ (-ONO_2).

Silver Nitrate Promoted Hydrolysis of 3.—1,*exo*-2-Dichloronorbornane (**3**) was treated with aqueous silver nitrate as described above. After 8 hr vpc analysis (SE-30, 130°) showed the presence of norcamphor and a small amount of unreacted **3**.

4-Chloronorcamphor (14) from 1-Chloro-3-*endo*-norbornanol (10).[8]—To a solution of 0.21 g of 10 in 0.7 ml of ether was added dropwise a solution of 0.15 g of sodium dichromate dihydrate and 0.11 ml of concentrated sulfuric acid in 0.75 ml of water. After 45 min at room temperature, 10 ml of ether was added. The organic phase was washed successively with aqueous sodium bicarbonate and water and dried over magnesium sulfate, and the solvent was removed at the rotary evaporator. Analysis by vpc showed two products (ratio of *ca.* 95:5). The major product was isolated by preparative vpc; its nmr and ir spectral properties and vpc retention time were identical with those of **14**,[18] except for the slight difference in carbonyl position already noted.

Solvolysis of 2,2-Dichloronorbornane (2).—A solution of 2.8025 g (17.10 mmol) of **2** and 2.3569 g (28.73 mmol) of sodium acetate trihydrate dissolved in 80% ethanol–20% water (v/v) was diluted to 100 ml in a volumetric flask. Aliquots (5 ml) were injected into soft glass ampoules which were then chilled, sealed under vacuum, and immersed in a constant-temperature bath at 70.0 ± 0.1°. Ampoules were titrated with 0.0200 *M* silver nitrate by Fajan's method, using dichlorofluorescein as indicator.[40] Analysis by vpc (SE-30, 125°) showed the products to be **6** (56 ± 1%) and **15** (44 ± 1%); the ratio was constant throughout the reaction.

Attempted Solvolysis of 1,*exo*-2-Dichloronorbornane (3).—A solution of 1.0 g of **3** in 20 ml of 80% ethanol was maintained at 85° for 480 hr. No liberated acid could be detected by titration with base. Analysis by vpc (SE-30, 140°) showed only **3**. Aliquots (5 ml) of a solution of 0.6943 g of **3** in 25 ml of 80% ethanol were sealed in ampoules as above. Titration of the ampoule opened after 795 hr indicated less than 0.2% reaction.

Attempted Solvolysis of 1,*exo*-3-Dichloronorbornane (4).—A solution of 1.6017 g (9.766 mmol) of **4** and 0.8040 g (9.800 mmol) of sodium acetate was diluted to 100 ml in 80% ethanol and sealed in ampoules as above. The contents of the ampoule titrated with 0.0100 *M* silver nitrate after 530.5 hr at 70° required 2.70 ml of titrant. The rate constant based on this titration (*ca.* 5% reaction) was based on the assumption that the impurity (0.4%) (*vide supra*) consisted of 2,2-dichloronorbornane **2**.

(40) H. H. Willard and N. H. Dean, "Elementary Quantitative Analysis," 3rd ed, D. Van Nostrand Co., New York, N. Y., 1940, p 169.

Registry No.—**2**, 19916-65-5; **3**, 15019-72-4; **4**, 19916-67-7; **5**, 15019-71-3; **6**, 694-93-9; **11**, 19916-70-2; **12**, 19916-71-3.

Acknowledgments.—Financial support by the National Science Foundation and by the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged. Professors P. von R. Schleyer and J. W. Wilt generously supplied preprints describing their studies, and Professor K. B. Wiberg kindly supplied spectral data for 1-chloro-3-norbornanone. W. B. F. was the recipient of a Wesleyan University 1967 Summer Study Grant. Professor B. Franzus carried out spin-decoupling experiments on **4** and made a number of helpful comments on the manuscript. Kinetic data were subjected to least-squares analysis on a General Electric time-sharing computer; Mr. Lee Riggs performed these analyses.

Cleavage of Hindered Aromatic Ethers. Kinetics[1]

CHARLES F. WILCOX, JR., AND MARGARET A. SEAGER

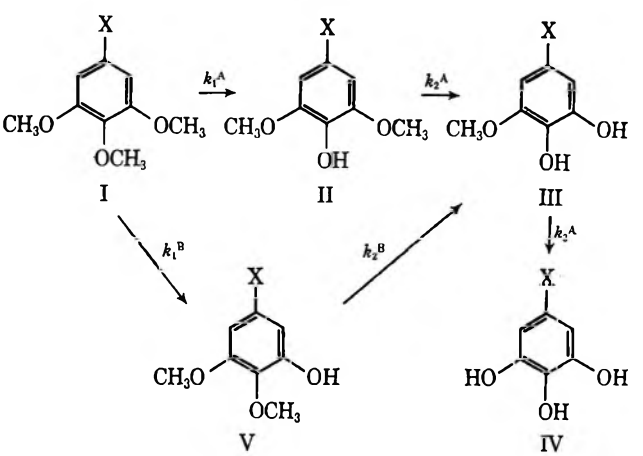
Department of Chemistry, Cornell University, Ithaca, New York 14850

Received November 20, 1968

The rates of ether cleavage by HBr in glacial acetic acid at 76° for trisethers and related monoethers are correlated by a $\rho\sigma$ plot. It is concluded that the enhanced rate of cleavage of 1,2,3-trimethoxybenzenes is too large to be accounted for by electrostatic substituent effects and occurs mainly because of the enhanced basicity of the central methoxyl as it is sterically twisted out of the plane of the benzene ring. The role of nonbonded interactions is discussed.

It is well known that trisethers with structure I, where X can be either an electron-attracting or electron-donating group, are cleaved by various acidic reagents to give largely II along with slight amounts of III and IV but little if any V[2-4] (Scheme I). Three different rationalizations can be offered. The generally accepted view[5] is that the middle methoxyl is crowded out of the plane of the benzene ring. This involves an unspecified combination of steric alteration of nonbonded interactions and enhanced basicity of the central methoxyl due to partial loss of conjugation. Brossi, *et al.*,[6] in discussing the ether cleavage of cactus alkaloid isoquinoline analogs of I, emphasized the second component involving enhanced basicity. A third possibility is that the rates are normal and determined solely by the accepted electromic effects of all ring substituents. Although much qualitative product data are available for this reaction, there are only

SCHEME I



(1) Taken in part from the M.S. dissertation submitted by M. A. Seager to the Cornell Graduate School, Sept 1966.

(2) W. J. Horton and J. T. Spence, *J. Amer. Chem. Soc.*, **77**, 2894 (1955); P. D. Gardner, W. J. Horton, and R. E. Pincock, *ibid.*, **78**, 2541 (1956).

(3) V. Prey, *Chem. Ber.*, **74**, 1219 (1941).

(4) M. T. Bogert and B. B. Coyne, *J. Amer. Chem. Soc.*, **51**, 569 (1929); M. Allen, A. L. Promislow, and R. Y. Moir, *J. Org. Chem.*, **26**, 2906 (1961).

(5) H. Thoms and W. Siebeling, *Chem. Ber.*, **44**, 2134 (1911).

(6) A. Brossi, M. Baumann, and R. Borer, *Monatsh. Chem.*, **96**, 25 (1965).

TABLE I
ETHER CLEAVAGE RATES IN HBr AND ACETIC ACID AT 76° OF X-SUBSTITUTED METHOXYBENZENES

Compd[a]	3-R[b]	4-R[b]	5-R[b]	1-X[b]	$\Sigma\sigma$	Rate[c] constant × 10^4
A_1	OCH_3	OCH_3	OCH_3	CH_3	−0.706	30.3
A_2	OCH_3	OH	OCH_3	CH_3	−0.320	2.0[d]
A_3	OH	OH	OCH_3	CH_3	−0.320	0.83
A_x	H	OCH_3	H	CH_3	−0.170	0.67
B_1	OCH_3	OCH_3	OCH_3	H	−0.536	19.6
B_2	OCH_3	OH	OCH_3	H	−0.255	1.33[d]
B_3	OH	OH	OCH_3	H	−0.255	0.55
B_x	H	OCH_3	H	H	0.000	0.38
C_1	OCH_3	OCH_3	OCH_3	$NHCOC_6H_5$	−0.458	19.3
D_1	OCH_3	OCH_3	OCH_3	$CH_2NEt_3^+$	−0.287	9.3
E_1	OCH_3	OCH_3	OCH_3	CHO	−0.320	6.7
F_1	OCH_3	OCH_3	OCH_3	CO_2H	−0.086	7.7
F_x	H	OCH_3	H	CO_2H	0.450	0.10
G_1	OCH_3	OCH_3	OCH_3	CN	0.124	3.3
H_1	OCH_3	OCH_3	OCH_3	NO_2	0.242	2.5
H_2	OCH_3	OH	OCH_3	NO_2	0.460	0.17[d]
H_x	H	OCH_3	H	NO_2	0.778	0.033
I_1	OCH_3	OCH_3	H	H	−0.268	4.0[d]
I_2	OH	OCH_3	H	H	−0.370	1.7

[a] These designations are keyed to Figure 1. [b] Substituents of 1,3,4,5-substituted benzenes; *e.g.*, A_1 is 3,4,5-trimethoxytoluene. [c] Rate constants are in moles per liter second. [d] This rate constant contains a statistical correction of 0.5.

fragmentary quantitative data and these do not permit a distinction between the above possibilities.

In keeping with our general interest in the transmission of substituent effects the present work was undertaken to obtain quantitative data on the rates of cleavage of the three methoxyl groups of trisethers, and to use these data to begin to unravel the factors leading to selective reaction of the central methoxyl. A plot of the kinetic data should give a single line if only electrostatic substituent effects are responsible while the incursion of special steric effects for the central methoxyl should reveal itself by the systematic enhancement of these rates over the "standard" nonaccelerated cleavage rates.

The study included a range of substituents in the simple trisethers of type I, as well as dimethoxybenzene, anisole, three *para*-substituted anisoles, and the three 6,7,8-trimethoxyisoquinolines used by Brossi. The reagent–solvent combination selected was hydrogen bromide in glacial acetic acid since it would give homogeneous reactions, is easily prepared, and cleaves these ethers at convenient rates.

Experimental Section[7]

Materials.—The hydrogen bromide in glacial acetic acid was prepared according to the procedure of Kolthoff and Bruckenstein.[8] The solution was stored at −20° until needed. Solutions of sodium acetate in glacial acetic acid were prepared by dissolving dried (110° for 5 hr) sodium acetate in commercial glacial acetic acid. The acetate solutions were standardized against 0.0977 *M* perchloric acid in acetic acid using *p*-naphtholbenzein as an indicator.[8]

N-Benzoyl-3,4,5-trimethoxyaniline.—To 3.7 g (0.02 mol) of 3,4,5-trimethoxyaniline in 70 ml of dry ethyl acetate was added 3.0 ml of benzoyl chloride and the mixture refluxed for 4 hr. The solvent was removed and the product was recrystallized from dilute ethanol to yield 4.2 g (90% yield) of gray crystals: mp 140°; nmr ($CDCl_3$, TMS), τ 2.72, 3.00, 3.28 (total of 7 H), and 6.46 (9 H).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.90; H, 5.92; N, 4.88. Found: C, 66.84; H, 5.77; N, 4.63.

3,4,5-Trimethoxybenzyltriethylammonium Bromide.—A solution of 5 ml of (0.050 mol) of triethylamine and 1.3 g (0.005 mol) of α-bromo-3,4,5-trimethoxytoluene in 25 ml of dry acetone was refluxed for 5 hr. The crystalline product was collected and washed repeatedly with acetone until it was pure white. From the analysis it appeared to be the monohydrate.

Anal. Calcd for $C_{16}H_{28}O_3NBr \cdot H_2O$: C, 50.53; H, 7.95; N, 3.68; Br, 21.01. Found: C, 50.30, 50.67; H, 7.68, 8.09; N, 3.90, 3.71; Br, 21.41, 21.28.

3,4,5-Trimethoxynitrobenzene was prepared[9] by nitration of pyrogallol trimethyl ether to give pale yellow crystals in 76% yield, mp 97–97.5° (lit.[9] mp 97°).

3,4,5-Trimethoxytoluene was prepared by Wolff–Kishner reduction of the available 3,4,5-trimethoxybenzaldehyde[10] and purified by preparative glpc on a 5% FFAP column.

The 6,7,8-Trimethoxyisoquinolines.—The 1-methyl-6,7,8-trimethoxyisoquinoline, 1-methyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline, and 1-methyl-6,7,8-trimethoxy-1,2,3,4-tetrohydroisoquinoline were experimental compounds from the laboratory of Hofmann-La Roche, Inc., Nutley, N. J.[11]

Other ethers studied in this work were purchased commercially and were repurified before use.

Kinetics and Analysis.—Aliquots (2.5 ml) of an acetic acid solution of an ether and hydrogen bromide were sealed into necked tubes and suspended in a constant-temperature bath at 76.0°. One tube, not placed in the bath, served as an initial point and was titrated immediately. At selected intervals a tube was removed from the bath, quenched in ice water, and a 2-ml aliquot of the contents titrated with sodium acetate in acetic acid using *p*-naphtholbenzein as an indicator.

The kinetic measurements and data analysis for trimethoxybenzene, trimethoxytoluene, and trimethoxynitrobenzene were carried out in two ways. In the first the ether concentration was 0.020 *M* and the HBr concentration was 0.090 *M*. The resulting data were analyzed by the procedure of French and McIntire.[12] This method converts consecutive second-order reactions containing a common order in one component into consecutive first-order reactions by using the time integral of the common component in place of time as the independent variable. The resulting pseudo-first-order data are then analyzed graphically to obtain k_1, k_2, and k_3. In the present situation the actual kinetic scheme is one of parallel consecutive reactions (still reducible to pseudo-first-order reactions). The graphically derived value

(7) Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were determined on an A-60 Varian spectrometer.

(8) I. M. Kolthoff and S. Bruckenstein, *J. Amer. Chem. Soc.*, **78**, 1 (1956).

(9) R. F. Collins and M. Davis, *J. Chem. Soc.*, 1863 (1961).

(10) Y. Asakina and M. Yasue, *Chem. Ber.*, **69**, 2327 (1936).

(11) We would like to thank Dr. A. Brossi of the Hofmann-La Roche Co. for making these experimental samples available to us.

(12) D. French and R. L. McIntire, *J. Amer. Chem. Soc.*, **72**, 5148 (1950).

of k_1 is the sum of the two rate constants for cleavage of one methoxyl from the trisether. The values of k_2 and k_3 are averages of the cleavage rate constants of bis- and monoethers, respectively, with weighting functions that are approximately the fraction of reaction proceeding by each path. Since both kinetic and product data indicate that cleavage of the central ether dominates the reaction (by a factor estimated to be 30:1), the observed k_1 corresponds fairly closely to k_1^A, the rate constant for the cleavage of the central ether. The precision of each k_1 is about $\pm 2\%$ which means that k_1^A should be about $0.97k_1$ with an uncertainty of no more than $\pm 5\%$. The value of k_2^A is less certain but is probably equal to about $0.9k_2$ with a combined uncertainty of less than $\pm 10\%$. The value of k_3^A should be essentially the same as the observed k_3. The measured k_1 and k_2 rate constants are collected in Table I. Also tabulated are the measured values of k_2 divided by a statistical correction factor of 2.

In the second method of obtaining the kinetic rate constants for the trimethoxybenzene, trimethoxytoluene, and trimethoxynitrobenzene the ether and HBr concentrations were both 0.0335 M. The data were analyzed for k_1 by the usual procedure for second-order kinetics with equal concentrations. The values of k_2 and k_3 were not obtained. The values of k_1 agreed within 1% of the values obtained by the first method.

The constants for the other trisethers and monoethers listed in Table I were obtained and analyzed by the second method. The constants for dimethoxybenzene were obtained by both methods. In general, duplicate kinetic runs gave rate constants that agreed within $\pm 5\%$. For 3,4,5-trimethoxybenzaldehyde, the worst case, the agreement was only $\pm 15\%$.

The French and McIntire kinetic analysis used above was applied to the isoquinoline ethers. Here the cleavage of the second ether group is relatively faster so that k_1^B makes a larger contribution to k_1. Estimates based on the $\rho\sigma$ treatment to be described as well as the product analysis[6] suggest that k_1^A for these ethers is approximately $0.8k_1$ and k_1^B is approximately $0.2k_1$. The derived kinetic constants for these ethers are collected without statistical corrections in Table II.

TABLE II
ETHER CLEAVAGE OF ISOQUINOLINES AT 76° IN EXCESS HBr

Compd	$k_1 \times 10^4$ [a]	$k_2 \times 10^4$ [a]	$k_3 \times 10^4$ [a]
VII	5.3	2.5	0.31
VIII	1.2	0.51	0.051
IX	1.1	0.36	0.039

[a] Units are liters per mole second.

Results and Discussion

It is generally accepted that aromatic ethers are cleaved in acid by equilibrium protonation of the ether oxygen followed by nucleophilic attack on the neighboring alkyl carbon to give methyl bromide and a phenol. Aliphatic ethers cleave similarly except that the resulting alcohol normally reacts further. In accordance with this mechanism, ether cleavage by hydrogen bromide in aqueous acetic acid has been reported[13] to be second order with respect to the halogen acid. However, Mayo, *et al.*,[14] found aliphatic ether cleavage to be first order in glacial acetic acid. As discussed below, the difference is that in this (low dielectric constant and anhydrous) solvent the hydrogen bromide exists as ion pairs which, under the prevailing halogen acid concentrations and ether basicity, effectively cancel a kinetic order in the halogen acid.

Kolthoff and Bruckenstein[8] have investigated the system of hydrogen bromide in acetic acid in its reaction with the weak base indicator, *p*-naphtholbenzein. They give eq 1 where K_i is the equilibrium constant for formation of ion pairs, and K_d is the equilibrium constant for the dissociation to free ions. They concluded that there are few free ions in solution. On this basis the detailed mechanism given by eq 2–5 can be written for the cleavage of the ethers.

$$HBr \overset{K_i^{HBr}}{\rightleftharpoons} H^+Br^- \overset{K_d^{HBr}}{\rightleftharpoons} H^+ + Br^- \quad (1)$$

$$\text{ether} + H^+Br^- \overset{K_i^{IHBr}}{\rightleftharpoons} \text{ether } H^+Br^- \quad (2)$$

$$\text{ether } H^+Br^- \overset{K_d^{IHBr}}{\rightleftharpoons} \text{ether } H^+ + Br^- \quad (3)$$

$$\text{ether } H^+ + Br^- \xrightarrow{k_2} \text{products} \quad (4)$$

$$\frac{d(\text{product})}{dt} = k_2[\text{ether } H^+][Br^-] \quad (5)$$

Substitution of eq 1, 2, and 3 into eq 5 yields eq 6. This can be expressed in terms of the experimentally

$$\frac{d(\text{product})}{dt} = k_2K_i^{HBr}K_i^{IHBr}K_d^{IHBr}[\text{ether}][HBr] \quad (6)$$

observable stoichiometric concentrations by means of eq 7 and 8. In these equations the concentrations of

$$[\text{ether}] = [\text{ether}]_{st} - [\text{ether } H^+Br^-] \quad (7)$$

$$[HBr] = [HBr]_{st} - [H^+Br^-] \quad (8)$$

dissociated ions have been neglected relative to the ion pairs and un-ionized species.[8]

The H_0 acidity function[15] for hydrogen bromide in glacial acetic acid, by a short extrapolation of the data reported by Smith and Elliot,[16] is -1.6 for the highest (3×10^{-2} M) acid used in this work. Aromatic ethers undergo both ring-carbon and oxygen protonation; Kresge and Hakka[17] have estimated that 1,3,5-trimethoxybenzene has an effective pK_a for C protonation of -3.7. Since this molecule should be a considerably stronger carbon base than the molecules included in this study diversion of ether by C protonation need not be considered here.

The question of oxygen protonation is somewhat more complex. Anisole has a $pK_a = -6.5$ while 5,5-dimethylhomochroman, in which the ether oxygen is held completely out of the plane of the benzene ring, has a $pK_a = -1.9$, typical of an aliphatic ether.[18] Since models suggest that the central methoxyl is only partially tipped out of the plane it is reasonable to suppose the parent pK_a for the central methoxy group lies closer to -6.5 than to -1.9. The basicity of the central methoxyl will be enhanced by the neighboring methoxyls but fragmentary data in the literature suggest this is less important than the steric effect.[19] It can be concluded that the trisethers in this study are predominantly in the unprotonated form. This receives partial support from the observation of an unchanged nmr spectrum for 3,4,5-trimethoxytoluene in glacial acetic acid with and without hydrogen bromide present. It is supported further by the relative constancy of the derived kinetic constants since the HBr

(13) R. L. Burwell, Jr., *Chem. Rev.*, **54**, 615 (1954).
(14) F. R. Mayo, W. B. Hardy, and C. G. Schultz, *J. Amer. Chem. Soc.*, **63**, 426 (1941).
(15) L. P. Hammett and A. J. Deyrup, *ibid.*, **54**, 2721 (1932).
(16) T. L. Smith and J. H. Elliott, *ibid.*, **75**, 3566 (1953).
(17) For an analysis of the protonation data and leading references to earlier work, see A. J. Kresge and L. E. Hakka, *ibid.*, **88**, 3868 (1966).
(18) E. M. Arnett and C. Y. Wu, *Chem. Ind.* (London), 1488 (1959).
(19) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1964).

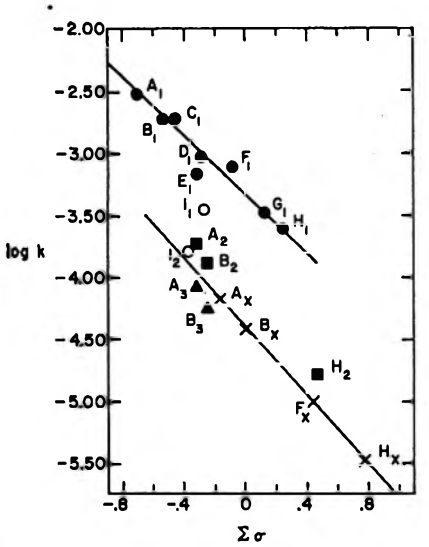


Figure 1.—Plot of log k *vs.* $\Sigma\sigma$ for all ethers in Table I: ●, cleavage of R_1 of trimethoxybenzenes; ■, cleavage of R_2 of trimethoxybenzenes; ▲, cleavage of R_3 of trimethoxybenzenes; ×, cleavage of monomethoxybenzenes; ○, cleavage of Veratrole.

concentration changes markedly during a kinetic run. On this basis eq 6 can be rewritten as eq 9.

$$\frac{d(\text{product})}{dt} = \frac{k_0 K_i^{HBr} K_i^{IHBr} K_d^{IHBr}}{1 + K_i^{HBr}} [\text{ether}]_{st}[HBr]_{st} \quad (9)$$

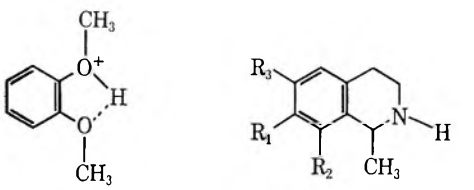
All experimental results were consistent with the cleavage reactions (see Experimental Section) being first order in stoichiometric ether and first order in stoichiometric hydrogen bromide. Consistent with this kinetic scheme, added bromide ion or added tosylic acid had no significant effect.

A $\rho\sigma$ plot of the entire set of data recorded in Table I is shown in Figure 1. Substituent constants[20] were available for all of the *para* substituents except $-CH_2N^+Et_3$ for which a value of $0.35 \times \sigma$ [p-$N^+(CH_3)_3$] was assigned.[21] The *o*-OCH_3 and *o*-OH substituents were assigned *p*-OCH_3 and *p*-OH σ constant values. As has been pointed out,[22] the few available *ortho* σ^* constants defined by Taft and used to fit ionization of *ortho*-substituted benzoic acids and other similar reactions[23] are nearly the same as the corresponding *para*-substituent constants. While these *ortho* constants may not characterize precisely the electronic effects involved in the ether cleavages, they would appear to be a reasonable approximation to them.

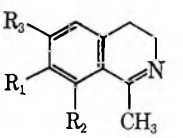
To the extent the σ values are in error, they presumably deviate in the direction of more positive values as a consequence of being closer to the reaction site and having a larger positive inductive component.[24]

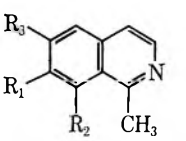
In Figure 1 the points marked × are for cleavages of the monomethoxybenzenes. These ethers, uncomplicated by special steric, solvent, or substituent effects, define an excellent regression line, log $k = (-1.36 \pm 0.01)\Sigma\sigma + (-4.41 \pm 0.01)$.[25] Clustered about this line are the rates for cleavage of the second (■) and the third (▲) methoxyls of the trisethers. With these additional values the regression line becomes log $k = (-1.32 \pm 0.05)\Sigma\sigma + (-4.36 \pm 0.07)$. On a regression line distinct from the first but of similar slope (log $k = (-1.13 \pm 0.04)\Sigma\sigma + (-3.33 \pm 0.05)$ are the rates of cleavage of the central methoxyls of the trisethers. The spread between these last two lines corresponds to a factor of 10 in cleavage rate. If the placement of the filled points on the lower line is accepted, Figure 1 represents good evidence that the cleavage of the central methoxyls of the trisethers is sterically enhanced relative to the cleavage rates of the flanking methoxyls. The 0.19 difference in slope between the two lines is statistically significant in the sense that with the observed standard deviations of each set of points there is less than 1% chance that another random sampling of ethers would give identical slopes. On the other hand the difference is so small that it could easily be accommodated by appeal to minor changes in the σ constants in the two sets or to variation in ρ from differences in solvation.

Important evidence for the correctness of this interpretation is provided by the entries (○ in Figure 1) for the cleavage of the first and second methoxyls of dimethoxybenzene. Unlike the trisethers, the methoxyls of dimethoxybenzene can be simultaneously coplanar and it would be expected that dimethoxybenzene should show a significantly enhanced rate by virtue of forming the more stable, internally hydrogen-bonded intermediate (VI). In terms of eq 9 this corresponds to a larger K_i^{IHBr} and K_d^{IHBr}. The cleavage rate of the second methoxyl of dimethoxybenzene has no unique structural feature and should fit on the lower regression line with the other unaccelerated ethers. As Figure 1 shows, these expectations are borne out.


VI

VII


VIII


IX

$R_1 = R_2 = R_3 = OCH_3$

The three cleavage rates of 1-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline, VII, are also consistent with the steric interpretation. Saturated rings fused to aromatic rings have similar effects as two appropriate groups attached to the same points of fusion.[26] In a strongly acidic medium the amine will be protonated so that for it the $-CH_2N^+R_3$ σ is appropri-

(20) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

(21) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1941.

(22) J. Hine, "Physical Organic Chemistry," 2nd ed., McGraw-Hill Book Co., Inc., New York, 1962.

(23) See R. W. Taft, Jr. in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, Chapter 13. For a recent evaluation of several *ortho* substituent constants, see G. G. Smith and K. K. Lum, *Chem. Commun.*, 1208 (1968).

(24) G. G. Smith, private communication, has found in several cases of ester pyrolyses that the *ortho* substituent constant for methoxyl is significantly more positive than the *para* constant.

(25) The deviations in the slope and intercept are standard deviations calculated in the conventional way by the unweighted least-squares method.

(26) G. B. Barlin and D. D. Perrin, *Quart. Rev.* (London), **20**, 75 (1966).

ate. An important difference in the isoquinoline series is the presence of the 1-methyl which forces the 8-methoxy out of the plane. This means that appropriate representation of the substituent effect of the 8-methoxyl toward cleavage of the central 7-methoxyl is given by a *meta* σ (OCH_3). Because of these same steric effects, the cleavage rate of the 8-methoxyl of the isoquinoline trisether is much faster than the simpler ethers represented in Table I. Estimates based on σ constants using a *meta* constant for a twisted *ortho* methoxyl, and the same steric acceleration factor of 10, yield a k_1^B that is one-third the value of k_1^A. It can be seen that k_1^A ($= k_1/1.33$) fits nicely on the upper line with the estimated $\Sigma\sigma = -0.02$.

These identical considerations indicate also that the cleavage rate, k_2, of the second methoxyl of VII should be much faster than the k_2 of the simpler ethers. The estimated value of k_2 of about 1.3×10^{-2} compares extremely well with the observed value of 1.5×10^{-2} and lends further support to the present interpretation.

The three cleavage rates of 1-methyl-6,7,8-trimethoxy-1,2-dihydroisoquinoline, VIII, and of 1-methyl-6,7,8-trimethoxyisoquinoline, IX, were also measured. Unfortunately the uncertainties in the electrostatic influence of the heteroatom do not permit an unambiguous placement of these points on the graph in Figure 1. Examination of the data will show, however, a good fit for any reasonable $\Sigma\sigma$. Furthermore, the k_1/k_2 ratios show the same expected high value as the tetrahydro derivative.

The preceding argument has been concerned with the consistency of the data using conventional *ortho* substituent constants. It is instructive to turn the argument around and consider first what changes in the analysis are required in order to have the points for the cleavages of the central methoxyls fall on the line defined by the *para*-substituted anisoles. The consequences for the placement of the other points must then be considered. Since the central methoxyls are flanked by two methoxyls, denial of the observed 0.8 σ unit spread requires that the *ortho* σ (OCH_3) be *more negative* by about 0.4 units. Such σ values would be exceptional but supporting arguments might be found.[27] The remaining compounds have only one *ortho* substituent and would be displaced by only 0.4 of a unit. Such an assignment happens to place around a single regression line all points of Table I except those for the cleavage of the third methoxyl of the trisethers, which are then in a unique position far below the new line. It might be hypothesized that these third ether groups are unique because of a retardation due to internal hydrogen bonding that is necessarily absent in the trisethers and in the hydroxydimethoxy ethers. However, the second methoxyl of dimethoxybenzene would also be hydrogen bonded; so its cleavage rate would then show an unexplained apparent acceleration. The cleavage rates of the second methoxyls of the isoquinoline ethers would present a further difficulty since with the modified σ constants and no steric acceleration these would also be too fast. Because of the difficulties created by this alternative rationalization we reject it in favor of invoking conventional substituent constants combined with steric acceleration of central methoxyls.

The conclusion that the tenfold rate enhancement of k_1 is primarily steric in origin brings more clearly into focus the question of the source of this steric effect. From the high basicity of 5,5-dimethylhomochroman it might have been expected that the k_1 rates would be enhanced by a factor nearer 10,000. That only a factor of 10 is visible suggests that nonbonded interactions may *increase* in going through the transition state. Since the configuration of the methyl group undergoing cleavage must invert, increased interactions would be expected if bond making to the entering nucleophile were advanced over bond breaking to the ether oxygen. This suggests that poorer nucleophiles, for which bond making would be still more advanced, might show a smaller net steric effect.

(27) The electrostatic field effect of the methoxyl could be quite dependent on the details of conformational averaging. Bias toward conformations with the lone pair electrons pointing toward the central methoxyl favors more negative σ values.

Conclusion

The enhanced cleavage rates of the central methoxyl of 1,2,3-trimethoxybenzene derivatives can be explained consistently and reasonably by invoking steric acceleration. It is estimated that the observed rate factor of 30 is composed of a factor of about 10 from steric acceleration and about 3 from substituent effects. An alternative explanation in terms of decreased basicity of the 1- and 3-methoxyls could account for most of the available data but only by postulating unprecedentedly negative *ortho* σ (OCH_3) constants.

Registry No.—N-Benzoyl-3,4,5-trimethoxyaniline, 19987-70-3; A_1, 6443-69-2; A_2, 6638-05-7; A_3, 1125-67-3; A_x, 104-93-8; B_1, 634-36-6; B_2, 91-10-1; B_3, 934-00-9; B_x, 100-66-3; C_1, 19987-70-3; D_1, 19978-23-5; E_1, 86-81-7; F_1, 118-41-2; F_x, 100-09-4; G_1, 1885-35-4; H_1, 6307-90-0; H_2, 19978-25-7; H_x, 100-17-4; I_1, 91-16-7; I_2, 90-05-1; VII, 3881-29-6; VIII, 4838-98-6; IX, 19978-28-0.

The Chemistry of Carbanions. XVIII. Preparation of Trimethylsilyl Enol Ethers[1a]

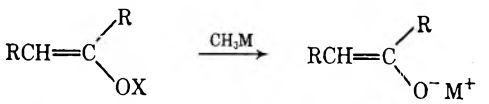
HERBERT O. HOUSE, LEONARD J. CZUBA,[1b] MARTIN GALL, AND HUGH D. OLMSTEAD[1c]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received November 26, 1968

Two procedures for the preparation of trimethylsilyl enol ethers from aldehydes and ketones are described. Reaction of the ketone with chlorotrimethylsilane and triethylamine in dimethylformamide solution usually affords an equilibrium mixture of the trimethylsilyl enol ethers. Successive reaction of the ketone with lithium diisopropylamide and with chlorotrimethylsilane in 1,2-dimethoxyethane solution normally produces a mixture in which the less highly substituted enol ether (from kinetically controlled enolate formation) is the principal product. A number of representative structurally and stereochemically isomeric trimethylsilyl enol ethers have been characterized (see Table II) and their physical properties have been studied.

In earlier studies[2] specific structural isomers and stereoisomers of enolate anions **1** were generated by reac-



2a, X = $COCH_3$
b, X = $Si(CH_3)_3$

1

tion of enol acetates **2a** with 2 equiv of methyllithium. One of the by-products of this reaction is the strongly basic lithium *t*-butoxide which may complicate subsequent alkylation of the enolate anions by promoting further alkylation of the initially formed product. In an effort to find a procedure which would produce specific enolate anions not accompanied by a strongly basic by-product, we were led to consider the reactions of enol derivatives of phosphorus,[3] tin,[4] and silicon[5] (*e.g.*, **2b**) with organometallic reagents. After preliminary experimentation, we concluded that the ease of syntheses and stability[6] of the trimethylsilyl enol ethers **2b** recommended these intermediates over the phosphorus and tin derivatives. The same conclusion was reached independently by Stork and Hudrlik, who recently published[5f] a preliminary account of their studies of silyl enol ethers with objectives similar to our own. In this paper are described the preparative methods that we employed and the characterization of various trimethylsilyl enol ether derivatives, including the conversion of a number of these silyl ethers into enolate anions and subsequently to enol acetates. A subsequent publication will describe our study of these materials as precursors for enolate anion intermediates in alkylation reactions.

The preparative methods previously employed[5] for silyl enol ethers have involved preliminary treatment of ketones with bases of sufficient strength to convert the ketones completely into their enolate anions; the bases which have been employed include sodium bis(trimethylsilyl)amide,[5a] the sodium radical anion of anthracene,[5d] sodium hydride,[5f] and triphenylmethylpotassium.[5f] Depending upon the way in which the ketone and base are mixed, either a kinetically controlled mixture of enolate anions or an equilibrium mixture of enolate anions may be obtained.[2,5f] Subsequent reaction of the enolate anion(s) with excess trimethylsilyl chloride has produced the silyl enol ethers in good yield.[5] Since we wished to use these silyl ethers, like the previously studied enol acetates,[2] for the preparation of specific structural isomers of unsymmetrical ketone enolates, as well as enolates of symmetrical ketones and aldehydes, considerable effort was expended in seeking synthetic methods which would produce the pure silyl ethers easily and in synthetically useful amounts. Of the various methods examined, the most satisfactory procedure for aldehydes and ketones which are symmetrical or which can enolize in only one direction involved direct reaction of the carbonyl compound with either triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) and excess trimethylsilyl chloride in dimethylformamide (DMF) solution. Typical examples are illustrated in Scheme I and the various reactions studied are summarized in Tables I and II. The enol ether products were readily isolated by fractional distillation, and could be stored without decomposition or hydrolysis provided that they were protected from water and, especially, aqueous acids. Our studies are consistent with the simple view that enol ether formation proceeds by reaction of the ketone with the amine to form an enolate anion which then reacts with the trimethylsilyl chloride to form the O-silylated product.

When the same preparative procedure was applied to unsymmetrical ketones capable of forming structurally isomeric enol ethers (Tables I and II), mixtures of structural isomers were obtained in all cases except with phenylacetone (**14**, Scheme II) and the octalone **28** where only the conjugated isomers **15**, **16**, and **29** were observed. The proportions of structural isomers present (*e.g.*, **22b** and **23b**, Scheme II) in the reaction mixtures was observed to change as the reaction progressed suggesting that the mixture of reagents triethylamine hydrochloride and trimethylsilyl chloride in dimethyl-

(1) (a) This research has been supported by Research Grant No. AFOSR-68-1518 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research, and by Public Health Service Research Grant No. 1-R01-CA10933-01 from the National Cancer Institute; (b) National Institutes of Health Postdoctoral Fellow, 1967–1968; (c) National Institutes of Health Predoctoral Fellow, 1966–1968.

(2) For a review, see H. O. House, *Rec. Chem. Progr.*, **28**, 99 (1967).

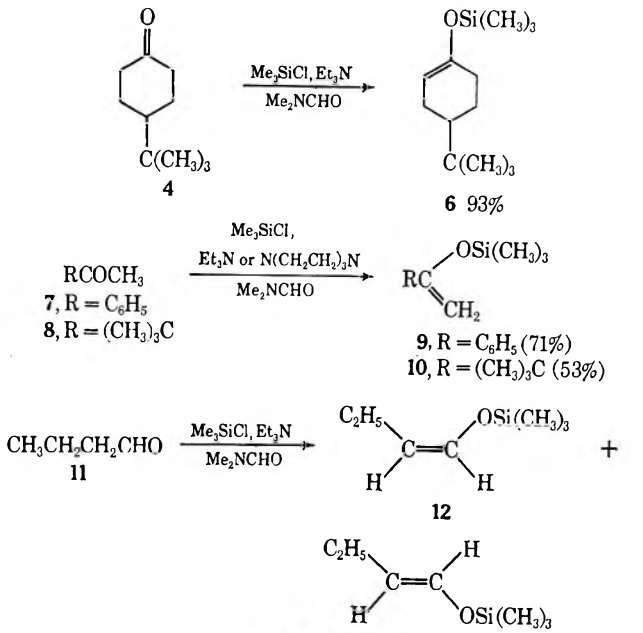
(3) For discussions of the preparation of enol phosphates, see (a) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); (b) P. S. Magee, *Tetrahedron Lett.*, 3995 (1965); (c) T. Mukaiyama, T. Kumamoto, and T. Nagaoka, *ibid.*, 5563 (1966).

(4) For a recent discussion of trialkyltin enol ethers, see M. Pereyre, B. Bellegarde, J. Mendelsohn, and J. Valade, *J. Organometal. Chem.*, **11**, 97 (1968).

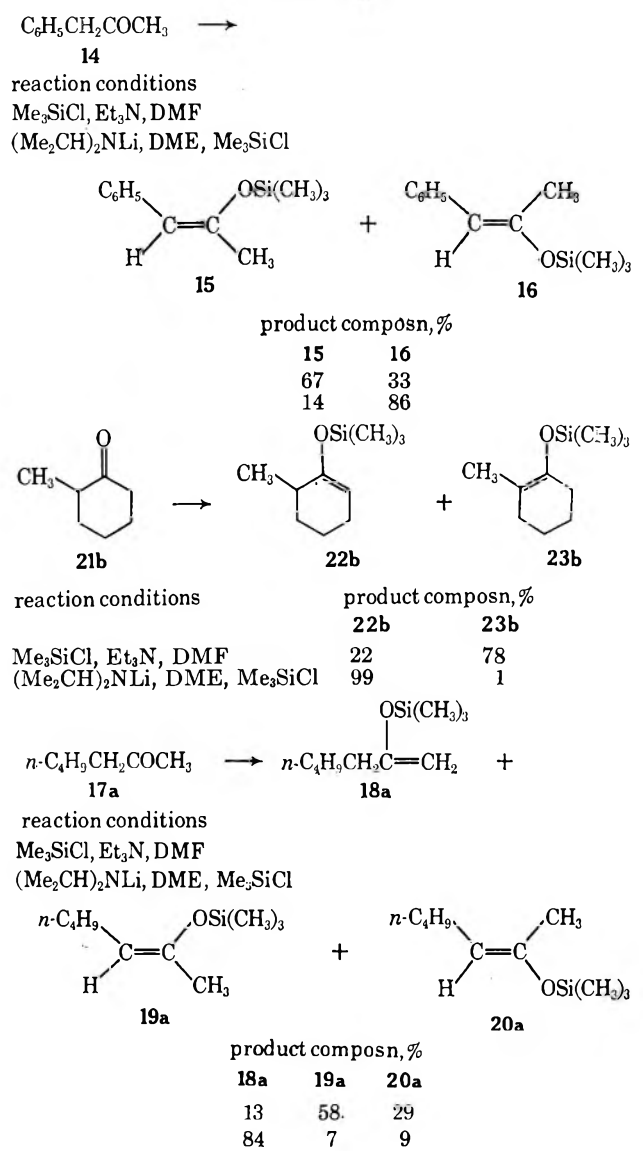
(5) For descriptions of the preparation of silyl enol ethers, see (a) C. R. Krüger and E. G. Rochow, *J. Organometal. Chem.*, **1**, 476 (1964); (b) J. I. Baukov, G. S. Burlachenko, and I. F. Lutsenko, *ibid.*, **3**, 478 (1965); (c) R. J. Fessenden and J. S. Fessenden, *J. Org. Chem.*, **32**, 3535 (1967); (d) R. Bourhis and G. Frainnet, *Bull. Soc. Chim. Fr.*, 3552 (1967); (e) U. Schmidt and M. Schwochan, *Tetrahedron Lett.*, 4491 (1967); (f) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968).

(6) For examples of the rearrangement of 2-silyl ketones to enol ethers, see (a) A. G. Brook, D. M. MacRae, and W. W. Limburg, *J. Amer. Chem. Soc.*, **89**, 5493 (1967); (b) I. F. Lutsenko, Yu. I. Baukov, O. V. Dudukina, and E. N. Kramarova, *J. Organometal. Chem.*, **11**, 35 (1968).

SCHEME I



SCHEME II



formamide solution would slowly isomerize the trimethylsilyl enol ethers to form an equilibrium mixture.

Further investigation established that these reaction conditions would equilibrate silyl enol ethers. In fact, this method of equilibration was the most satisfactory procedure that we found. In our hands, the use of acids such as anhydrous *p*-toluenesulfonic acid (recommended by Stork and Hudrlik[5f]), anhydrous hydrogen chloride, or trifluoroacetic acid was seriously complicated by the concurrent formation of substantial amounts of higher molecular weight materials and ketones (from a hydrolytic or related cleavage of the silyl enol ethers). The equilibrations were complicated by concurrent formation of some ketone even when the silyl enol ethers were treated with trimethylsilyl chloride and triethylamine hydrochloride in dimethylformamide. However, we were able to establish equilibrium more rapidly than the enol ethers were cleaved and obtained the approximate equilibrium data for trimethylsilyl enol ethers presented in Scheme III. (A mixture containing 9% **22b** and 91% **23b** was observed by Stork and Hudrlik after treatment of the silyl ethers with toluenesulfonic acid.) In Scheme III, these equilibrium compositions are compared with earlier data obtained by the acid-catalyzed equilibration[7] of the analogous enol acetates and enol ethers to illustrate the apparent trend for the silyl ethers to have equilibrium compositions similar to or in between the equilibrium compositions of the corresponding enol ethers and enol acetates (*cf.* ref 5f). In instances where an equilibrium mixture of trimethylsilyl enol ethers is desired for preparative work, we recommend use of a prolonged heating period during the reaction of the ketone with trimethylsilyl chloride and triethylamine in dimethylformamide.

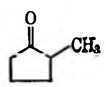
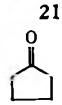
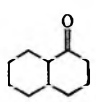
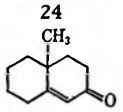
It was apparent that the less highly substituted silyl enol ethers (*e.g.*, **18a** and **22b**, Scheme II) could be obtained more efficiently by the initial reaction of the ketones with a strong base under conditions of kinetically controlled deprotonation.[2,5f] Further reaction with trimethylsilyl chloride would produce the desired enol ethers (*cf.* ref 5f). Although triphenylmethyllithium or triphenylmethylpotassium might be used for this purpose, the presence of substantial amounts of triphenylmethane in a reaction mixture complicates product isolation. The relatively slow reaction of a ketone with sodium hydride[5f] to produce an enolate solution normally affords an equilibrium mixture of enolates and is often complicated by the concurrent formation of aldol products.[2] Our attempts to obtain silyl ethers by reaction of ketones with sodium hydride in the presence of excess trimethylsilyl chloride to trap the enolate anions as formed were uniformly unsuccessful. This observation is in keeping with the common supposition that traces of alcohols (and the corresponding alkoxides) are the usual proton transfer agents in reactions of ketones with the insoluble polymeric sodium hydride. Since the trimethylsilyl chloride would be an excellent scavenger for traces of alkoxides,[8] the absence of any reaction between the ketones and sodium hydride under these conditions is understandable.

(7) (a) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); (b) H. O. House and B. M. Trost, *ibid.*, **30**, 1341, 2502 (1965).

(8) The use of trimethylsilyl chloride as a scavenger for alkoxides has been used to advantage in the acyloin condensation. See (a) J. J. Bloomfield, *Tetrahedron Lett.*, 587, 591 (1968); (b) G. E. Gream and S. Worthley, *ibid.*, 3319 (1968).

TABLE I

CONVERSION OF KETONES INTO SILYL ENOL ETHERS

Ketone	Preparative method[a] (reaction time, hr)	Yield of enol ether(s), % [bp, n^tD for product]	Enol ether product (composn, %) listed in order of elution on gas chromatography
 **3**	A (4.0)	70 [74–75° (20 mm), n^{24}D 1.4451]	**5** (>98)[b]
4	A (18.0)	93 [94–96° (3.9 mm), n^{22}D 1.4549]	**6** (>98)[b]
7	A (19.0)	71 [89–91° (12 mm), n^{26}D 1.4988]	**9** (>98)[c]
8	A (6.0)[d]	53 [140–142° (760 mm), n^{27}D 1.4061]	**10** (>98)[e]
11	A (4.0)	59 [56–62° (75 mm), n^{25}D 1.4042–1.4071]	**12** (62), **13** (38)[e]
14	A (13.5)	42 [106° (10 mm), n^{20}D 1.5142–1.5149]	**16** (33), **15** (67)[f]
	B	34 [106–110° (10 mm)]	**16** (86), **15** (14)[f]
	C[g]	61 [81° (2.0 mm), n^{24}D 1.5140–1.5149]	**16** (4), **15** (96)[f]
17a	A (60)	52 [94–95° (52 mm), n^{25}D 1.4207–1.4224]	**18a** (13), **19a** (58), **20a** (29)[h]
	B	65 [104–106° (35–36 mm), n^{25}D 1.4178][i]	**18a** (84), **19a** (7), **20a** (9)[h,i]
$CH_3CH_2COCH_3$ **17b**	A (16)	77 [115–123° (760 mm), n^{25}D 1.4057]	**18b** (12), **19b** (64), **20b** (24)[e]
	B[j]	23 [100–130° (760 mm)]	**18b** (71), **19b** (13), **20b** (16)[e]
 **21a**	A (4.0)	69 [73–78° (34 mm), n^{25}D 1.4336–1.4392]	**22a** (43), **23a** (57)[e]
 **34**	A (8.0)	59 [158–159° (760 mm), n^{25}D 1.4377]	**35** (>98)[e]
$(CH_3)_2CHCOCH_2CH_3$ **30**	A (54)	50 [72–76° (58 mm), n^{25}D 1.4137–1.4220]	**33** (20), **32** (62), **31** (18)[e,h]
	B	87 [94–97° (88 mm), n^{25}D 1.4169]	**33** (53), **32** (42), **31** (5)[e,h]
21b	A (48.0)	80 [90–93° (20 mm)]	**22b** (22), **23b** (78)[b]
	B	74 [59–61° (7 mm), n^{22}D 1.4440]	**22b** (99), **23b** (1)[b]
 **24**	A (30)	86 [74–86° (0.4 mm), n^{25}D 1.4760]	**25** (17), **26** (5), **27** (78)[f]
	B	81 [75–87° (0.03 mm), n^{26}D 1.4737]	**25** (71), **26** (27), **27** (2)[f]
 **28**	A (23)	65 [95.5–98° (1.3 mm), n^{24}D 1.5008–1.5025]	**29** (>98)[e]
	B	47[...][e]	**29** (>98)[e]

[a] In procedure A, the ketone was treated with a mixture of Et_3N and Me_3SiCl. In procedure B, the enolate, formed by initial reaction of the ketone with $(i\text{-Pr})_2NLi$ in 1,2-dimethoxyethane, was treated with excess Me_3SiCl. [b] A gas chromatography column packed with Apiezon M suspended on Chromosorb G was employed for this analysis. [c] A gas chromatography column packed with nitrile gum, no. XE-60, suspended on Chromosorb P was employed for the analysis. [d] In this preparation, 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as the base instead of Et_3N. When Et_3N was used, the yield of silyl ether was 44%: bp 141–143°; n^{21}D 1.4090. [e] A gas chromatography column packed with silicone fluid, no. 710, suspended on either Chromosorb P or Chromosorb W was employed for this analysis. [f] A gas chromatography column packed with 1,2,3-tris(β-cyanoethoxy)propane suspended on Chromosorb P was employed for this analysis. [g] In this case, the enolate was prepared by reaction of the ketone with NaH and then treated with Me_3SiCl. In a small-scale reaction containing naphthalene as an internal standard, gas chromatographic analysis indicated that the silyl ether mixture was formed in 90% yield and contained 4% **16** and 96% **15**. [h] A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis. [i] In this case the distilled product mixture contained 5% unidentified impurity in addition to the silyl ethers indicated. [j] In this case the enolate was formed in diethylene glycol dimethyl ether rather than 1,2-dimethoxyethane to simplify separation of the volatile enol ethers.

TABLE II

CHARACTERIZATION AND PROPERTIES OF THE SILYL ENOL ETHERS

Structure	Bp, °C (mm)[a] [n^tD (t, °C)]	$\bar{\nu}_{C=C}$ (CCl_4), cm^{-1}	Nmr spectrum, δ values in CCl_4 soln (splitting)[b] Vinyl CH	Other[c]	Mass spectrum, m/e values (% of base peak) Abundant peaks and molecular ion (relative intensity)	Metastable peaks
5[d]	74–75 (20) [1.4451 (24)]	1670	4.73 (m)		170 (56), 155 (40), 127 (33), 75 (100), 73 (52)	113.6, 141.7, 169.5
*6[e,v]	98 (4.2) [1.4547 (22)]	1670	5.65 (m)	1.87 (*s*, *t*-butyl)	226 (10), 211 (33), 169 (18), 147 (58), 142 (30), 127 (26), 75 (100), 73 (40)	197.0, 113.7
9[f]	89–91 (12) [1.4988 (26)]	1620	4.27 (*d*, J = 1.7), 4.73 (*d*, J = 1.7)	7.05 (m, *m* and *p*-H), 7.34 (m, *o*-H)	192 (22), 147 (100), 191 (32), 75 (47), 177 (28), 73 (20)	163.4
*10[g]	140–141 (760) [1.4061 (27)]	1625 (s), 1665 (w)	3.78 (d, J = 1.4), 3.93 (d, J = 1.4)	1.02 (s, *t*-Bu)	172 (20), 157 (100), 75 (83), 73 (75), 44 (45)	143.3, 35.9, 34.0
*12[h]	56 (75) [1.4042 (25)]	1655	4.35 (d of *t*, J = 6.1 and 7.3), 5.97 (d of t, J = 6.1 and 1.3)	2.03 (m, CH_2), 0.90 (t, Me, J = 7.5)	144 (37), 129 (90), 75 (79), 73 (100)	115.6, 43.7, 41.3
*13[i]	62 (75) [1.4071 (25)]	1665	4.90 (d of t, J = 12.1 and 7.1), 6.12 (d of t, J = 12.1 and 1.3)	2.83 (m, methylene), 0.95 (t, Me, J = 7.1)	144 (36), 129 (84), 75 (85), 73 (100)	115.6, 43.7, 41.3
*15[j]		1654	5.41 (s, broad)	1.98 (d, Me, J = 0.8)	206 (100), 191 (35), 75 (22), 73 (78)	177.2, 156.8, 29.5, 27.8, 26.0
*16[k]		1651	5.71 (s, broad)	1.84 (d, Me, J = 0.8)	206(100), 191 (55), 75 (37), 73 (95)	177.1, 156.8, 29.5, 27.8, 26.0
*18a[m]		1654 (m), 1632 (s), 1617 (s)	3.93 (s)		186 (19), 171 (21), 144 (19), 143 (97), 130 (95), 115 (100), 75 (75), 73 (53), 45 (21), 43 (29)	27.7, 29.4, 37.3, 90.9, 101.8
*19a[m]	92 (50–52) [1.4225 (21.5)]	1675 (s)	4.36 (t, J = 6.8)[l]	1.73 (s, broad, vinyl Me)[l]	186 (12), 144 (15), 143 (95), 130 (15), 75 (31), 73 (100)	37.3, 32.9, 110.0
*20a[m]	94 (52) [1.4224 (25)]	1668 (s)	4.53 (t, J = 7.3)[l]	1.68 (s, broad, vinyl Me)[l]	186 (11), 144 (13), 143 (92), 75 (29), 73 (100)	37.3, 32.9, 110.0

TABLE II (*Continued*)

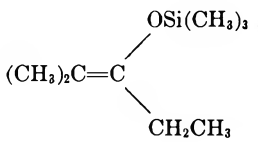
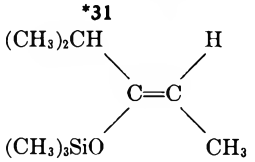
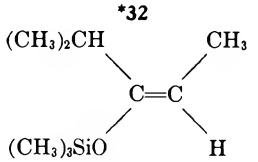
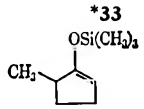
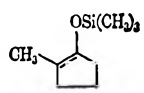
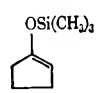
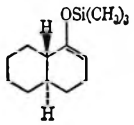
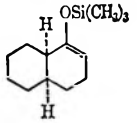
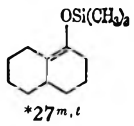
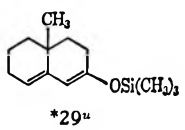
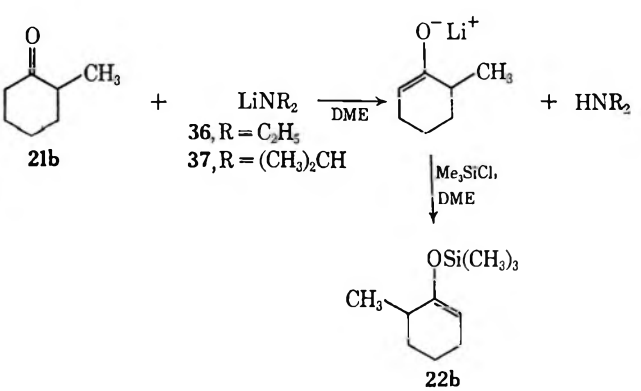
Structure	Bp, °C (mm)[a] [n^tD (*t*, °C)]	$\bar{\nu}_{C=C}$ (CCl_4), cm^{-1}	Nmr spectrum, δ values in CCl_4 soln (splitting)[b] Vinyl CH	Other[c]	Mass spectrum, *m/e* values (% of base peak) Abundant peaks and molecular ion (relative intensity)	Metastable peaks
$CH_3CH_2COSi(CH_3)_3$ $\parallel$ CH_2 ***18b**	108–110 (760) [1.4008 (26)]	1635 (s), 1660 (w)	3.92 (s)	1.00 (t, Me, J = 7.5), 2.00 (q, CH_2, J = 7.5)	144 (50), 129 (77), 75 (100), 73 (46)	43.6, 115.6
***19b**		1685	4.41 (q of q, J = 0.88 and 6.6)	1.43 (d of q, Me, J = 1.4 and 6.6), 1.61 (overlapping q's, Me)	144 (34), 119 (40), 75 (100), 73 (57)	43.5, 115.7
20b		1675	4.53 (q of q, J = 0.94 and 6.7)	1.51 (d of q, Me, J = 1.0, and 7.0), 1.67 (overlapping q's, Me)	144 (32), 119 (40), 75 (100), 73 (58)	43.5, 115.7
 ***31**		1678 (s)		1.58 (s, vinyl Me), 1.52 (s, vinyl Me), 0.98 (t, Me, J = 7.3)	172 (47), 157 (42), 75 (84), 73 (100), 45 (15),	33.9, 35.8 119.0 120.7, 143.3
 ***32**		1675 (s)	4.46 (q of d, J = 6.8 and 0.8)	1.47 (d of d, vinyl Me, J = 7.1 and 1.0), 1.01 (d, Me, J = 6.8)	172 (41), 157 (27), 75 (100), 73 (93), 45 (14)	33.9, 35.8, 119.0, 120.7, 143,3
 ***33**		1663 (s)	4.37 (q, J = 6.8)	1.52 (d, vinyl Me, J = 6.8), 0.93 (d, Me, J = 6.8)	172 (42), 157 (37), 75 (100), 73 (95), 45 (15)	33.9, 35.8, 119.0, 120.7, 143.3
 ***22a**[m]	73 (34) [1.4336 (25)]	1644 (s)	4.43 (m)	0.96 (d, Me, J = 6.5)	170 (37), 169 (28), 155 (36), 75 (100), 73 (97), 45 (19)	34.6, 36.3, 141.7
 ***23a**[m]	78 (34) [1.4392 (25)]	1690 (s)		1.48 (m, Me)	170 (61), 155 (61), 75 (76), 73 (100), 45 (19)	34.5, 36.3, 141.6
 ***35**[n]	158–159 (760) [1.4377 (25)]	1645	4.52 (m)		156 (68), 155 (27), 75 (98), 73 (100), 59 (42), 55 (35), 45 (91), 43 (65), 41 (32), 39 (51)	155.5, 141.5, 73.5, 39.8, 27.7
***22b**[m,o]	59–61 (7) [1.4440 (22)]	1665	4.58 (t, J = 3.3)	0.98 (d, Me, J = 6.5)	184 (98), 169 (74), 156 (24), 142 (43), 127 (29), 75 (85), 73 (100)	155, 103.5, 31.5, 27.7
***23b**[m,p]	101–102 (45) [1.4480 (25)]	1685		1.52 (broad, s, Me)	184 (86), 169 (100), 156 (19), 155 (20), 141 (47), 75 (79), 73 (97)	155.2, 131, 127.5, 31.7

TABLE II (*Continued*)

Structure	Bp, °C (mm)[a] [n^tD (t, °C)]	$\bar{\nu}_{C=C}$ (CCl4), cm^{-1}	Nmr spectrum, δ values in CCl4 soln (splitting)[b] Vinyl CH	Other[c]	Mass spectrum, m/e values (% of base peak) Abundant peaks and molecular ion (relative intensity)	Metastable peaks
 *25[m,q]		1660	4.60 (m)		224 (9), 147 (22), 75 (100), 73 (18)	29.4
 *26[m,r]		1660	s		224 (6), 186 (8), 147 (27), 77 (20), 75 (100), 73 (14)	
 *27[m,t]		1675			224 (40), 195 (25), 182 (25), 181 (24), 156 (22), 134 (32), 91 (23), 75 (61), 73 (100), 45 (43)	148, 105.8, 63.3, 27.8
 *29[u]	98 (1.3) [1.5009 (24)]	1680 (w), 1650 (s), 1625 (s)	5.10 (m)	0.98 (s, Me)	236 (76), 221 (44), 208 (25), 91 (57), 75 (29), 73 (100), 45 (40), 41 (28)	207.3, 179.1, 27.7

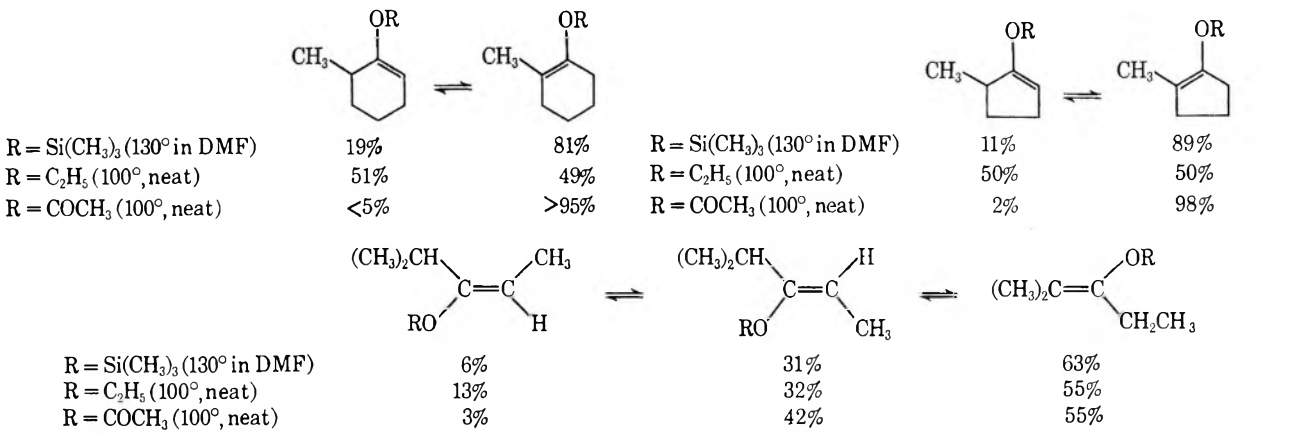
[a] No data are listed in cases where the pure silyl ether was isolated by collection from a gas chromatography column. [b] The abbreviations used are s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. All coupling constants, J, are given in hertz (cycles per second). [c] Broad multiplets are not listed in this table. Also a sharp singlet attributable to the 9 H of the $(CH_3)_3SiO$ found in each spectrum within the range δ 0.13–0.25 is not listed. [d] Ultraviolet end absorption (95% EtOH), ε 1835 at 210 mμ [lit. bp 58–58.5° (11 mm), n^{20}D 1.4452 (ref 5a), and bp 77.5° (28 mm), n^{20}D 1.4467 (ref 5d). [e] Ultraviolet end absorption (isooctane), ε 1340 at 220 mμ. [f] Lit. bp 93–94° (13.5 mm), n^{20}D 1.5008 (ref 5a), and bp 110° (28 mm), n^{20}D 1.5011 (ref 5d). [g] Lit. bp 138° (760 mm), n^{20}D 1.4105 (ref 5d). [h] Ultraviolet end absorption (isooctane), ε 475 at 220 mμ. [i] Ultraviolet end absorption (isooctane), ε 532 at 220 mμ. [j] Ultraviolet maximum (95% EtOH), 258 mμ (ε 19,200). [k] Ultraviolet maximum (95% EtOH), 253.5 mμ (ε 15,400) with a shoulder at 285.5 mμ (ε 1490). [l] In each of these peaks a further long-range coupling of approximately 0.8 Hz was partially resolved. [m] A mixture of silyl ethers containing this product has been described (ref 5f). The reported spectral values for the isomer **22b** were ir 1661 cm^{-1}; nmr δ 4.65 (m), 0.97 (d), and 0.15 (s). [n] Ultraviolet end absorption (95% EtOH), ε 1210 at 220 mμ. [o] Ultraviolet end absorption (95% EtOH), ε 2280 at 210 mμ. [p] Lit.[5f] bp 78–79° (17 mm); ir 1686 cm^{-1}; nmr δ 1.55 (s) and 0.16 (s). Ultraviolet end absorption (95% EtOH), ε 2980 at 210 mμ. [q] Ultraviolet end absorption (95% EtOH), ε 2850 at 210 mμ. [r] Ultraviolet end absorption (95% EtOH), ε 2650 at 210 mμ. [s] An insufficient amount of this isomer was isolated in pure form to obtain a satisfactory nmr spectrum. [t] Ultraviolet end absorption (95% EtOH), ε 6320 at 210 mμ. [u] Ultraviolet maximum (95% EtOH), 240.5 mμ (ε 20,800) with a shoulder at 283 mμ (ε 232). [v] Each of the silyl enol ethers marked with an asterisk (*) has been analyzed for carbon and hydrogen. In all cases the analytical values agreed with the calculated values to within ±0.30%; the actual analytical data were made available to the editors and referees.

We therefore turned to the lithium dialkylamides in 1,2-dimethoxyethane (DME) solution as bases capable of converting ketones into enolate anions under conditions of kinetic control.[7b] Although the usual reagent, lithium diethylamide (**36**), was not satisfactory because of subsequent reaction of the diethylamine with the silyl chloride, the more hindered diisopropylamide **37** was satisfactory. In this way the preparations of a number (Tables I and II) of the less highly substituted silyl ethers were accomplished as exemplified in Scheme II. In certain cases (see Experimental Section) involving methyl ketones (*e.g.*, **17**), aldol by-products were observed to result even from the slow addition of the ketones **17** to a solution of the lithium amide **37**. Evidently, in these cases, the rate of aldol condensation is competitive either with the rate of proton abstraction or with the rate of mixing of the reactants.



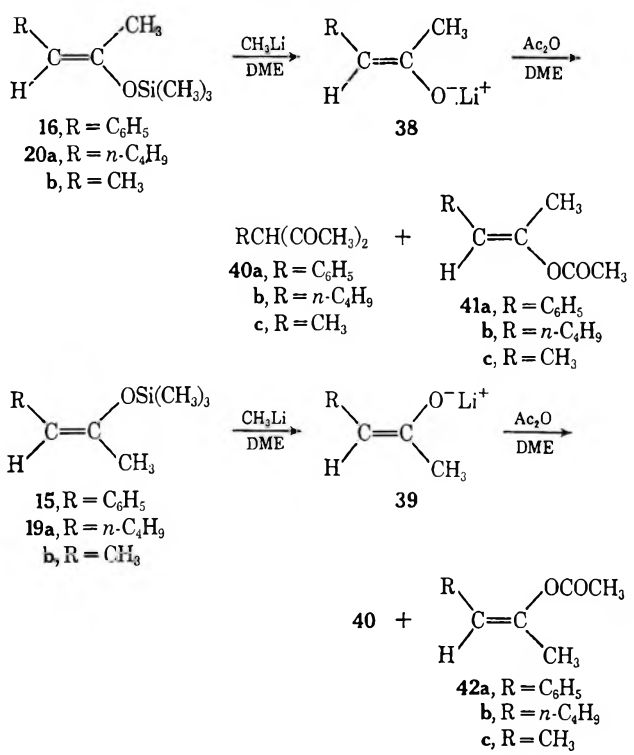
It is interesting to note that reaction with the amide base **37** not only favors formation of the kinetically favored (and usually less substituted) structural enolate

SCHEME III



isomer, but also favors slightly the formation of *cis* enolate anion **38** rather than the *trans* isomer **39**. Several of the *cis* (*e.g.*, **12**, **16**, **20a**, and **20b**) and *trans* (*e.g.*, **13**, **15**, **19a**, and **19b**) silyl ethers were converted into the corresponding enolates **38** and **39**, and then into the enol acetates **41** and **42**, as illustrated in Scheme IV. This

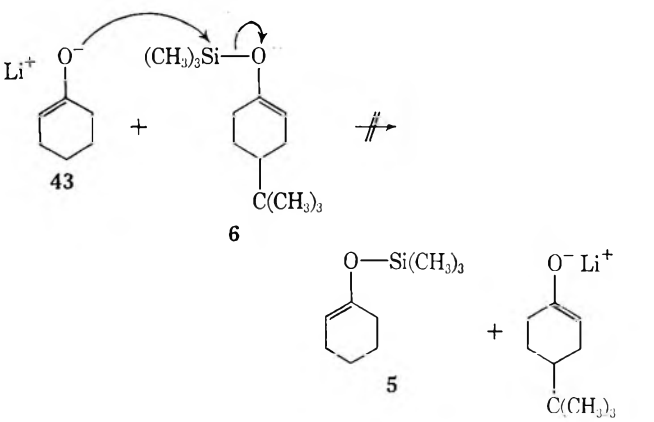
SCHEME IV



transformation served to interrelate the stereoisomeric silyl ethers with the known[7] enol acetate stereoisomers. We had noted earlier[7a,9] that the position of the nmr peak for the β-vinyl proton of enol ethers and enol acetates in benzene solution is helpful in assigning stereochemistry. In the isomer with the β-vinyl proton and oxygen function *cis* (*e.g.*, **41**) the position of the vinyl proton resonance is at lower field by 0.2–0.3 ppm than is the case when the oxygen function and β-vinyl proton are *trans* (*e.g.*, **42**). As illustrated in Table III, this same generalization appears to be applicable to the trimethylsilyl enol ethers, the only exception being a sterically crowded system **32** and **33**, in which the positions of the vinyl proton peaks are very similar.

We also note in passing that reaction of the *cis* enolate anions **38** with acetic anhydride gives significantly more C-acylated product than is observed on acetylation of the *trans* enolate anions **39**. Further discussion of this and related observations will be presented elsewhere.

To examine the possibility that silyl ethers might undergo equilibration with enolate anions by attack of the enolate oxygen at silicon a mixture of the silyl enol ether



6 and the enolate anion **43** was prepared, allowed to stand for 1 hr, and then quenched in water. None of the silyl ether **5** was detected. Consequently, formation of the silyl enol ether in the presence of enolate anions and the reverse process can be performed in 1,2-dimethoxyethane solution without concern for equilibration of the trimethylsilyl function.

Mass Spectra of the Trimethylsilyl Enol Ethers.—A recent investigation[10] of the mass spectral fragmentation of alkyl trimethylsilyl ethers indicated the importance of the general fragmentation pattern illustrated in Scheme V. Examination of the mass spectra (Table II) obtained from the trimethylsilyl enol ethers prepared in this study indicated both similarities and differences from the fragmentation pattern noted (Scheme V) for alkyl ethers. Stork and Hudrlik also observed[5f] abundant fragment peaks in the mass spectrum of the silyl enol ether **23b** at M − 15, 75, and 73.

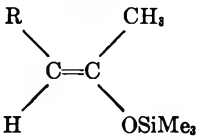
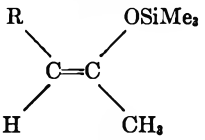
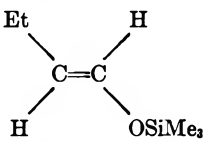
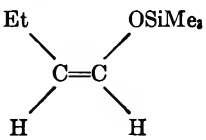
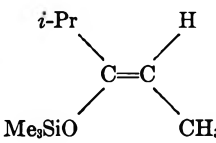
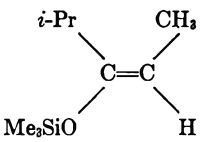
Since the mass spectrum of the silyl enol ether **20a** was typical of the mass spectra of the acyclic enol ethers

(9) A. comparable correlation for enol ethers in carbon tetrachloride solution was noted by F. Bohlmann, C. Arndt, and J. Starnick, *Tetrahedron Lett.*, No. 24, 1605 (1963).

(10) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **32**, 3904 (1967).

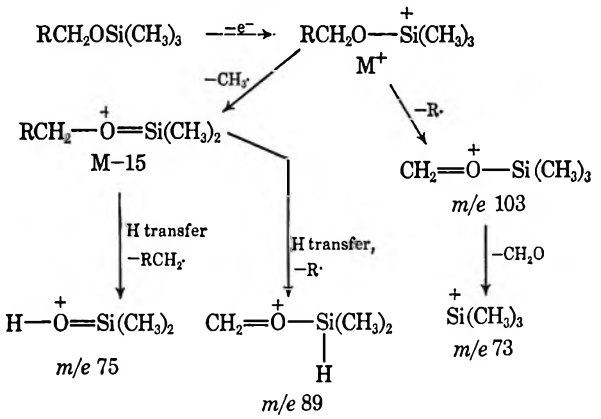
TABLE III

CHEMICAL SHIFT DIFFERENCES IN THE β-VINYL PROTON NMR SIGNAL FOR STEREOISOMERIC TRIMETHYLSILYL ENOL ETHERS

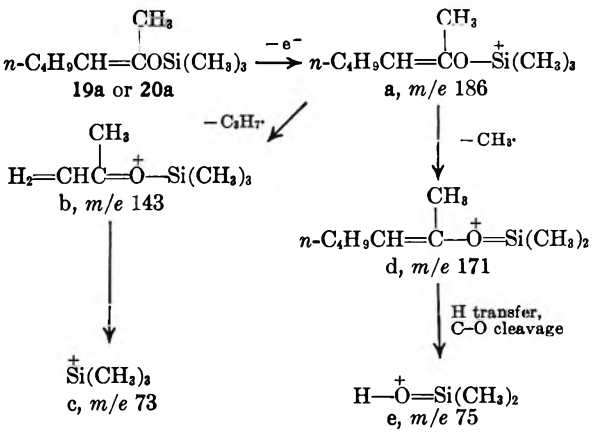
Isomer at lower field	Isomer at higher field	Δδ Benzene soln[a]	Δδ CCl_4 soln[a]
			
20a, R = *n*-Bu	**19a**, R = *n*-Bu	0.29	0.18
16, R = Ph	**15**, R = Ph	0.55	0.43
20b, R = Me	**19b**, R = Me	0.23	0.15
			
13	**12**	0.58	0.38
			
32	**33**	0.02	0.06

[a] These chemical shift differences were obtained from measurements made with solutions containing known amounts of each of the stereoisomeric enol ethers.

SCHEME V



SCHEME VI



studied, we selected this compound for the high resolution mass measurements summarized in Table IV.[11]

TABLE IV

HIGH RESOLUTION MASS MEASUREMENTS ON THE TRIMETHYLSILYL ENOL ETHER **20a**

Ion	Composn	Mass units Calcd	Mass units Found
a	$C_{10}H_{22}OSi$	186.1439	186.1446
d	$C_9H_{19}OSi$	171.1205	171.1208
b	$C_7H_{15}OSi$	143.0897	143.0892
e	C_2H_7OSi	75.0266	75.0259
c	C_3H_9Si	73.0474	73.0459

The general fragmentation pattern which we believe operative for the acyclic trimethylsilyl enol ethers studied is illustrated in Scheme VI for the ethers **19a** and **20a** which have very similar mass spectra.

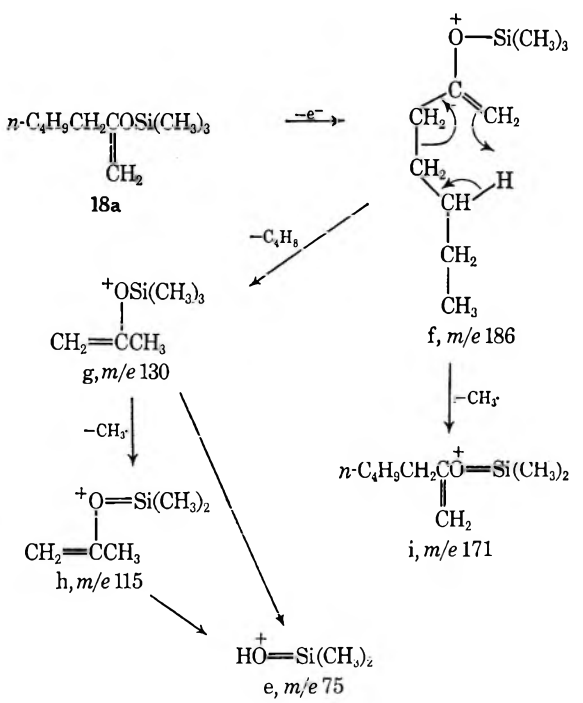
The allylic cleavage a → b (Scheme VI) in the *trans* isomer **19a**, a process vinylogous to a process observed for alkyl silyl ethers (Scheme V), is consistent with a metastable peak at *m/e* 110.0 (calcd $143^2/186 = 110.0$). Although we found no evidence from metastable peaks to indicate the direct formation of the trimethylsilyl ion c (*m/e* 73) from the parent ion a, a metastable peak at *m/e* 37.3 (calcd $73^2/143 = 37.3$) provides evidence for the cleavage b → c (Scheme VI) which finds analogy in the fragmentation of the alkyl silyl ethers (Scheme V). Analogous metastable peaks consistent with the sequence a → b → c are found in the spectra (Table II) of most of the silyl ethers where an allylic cleavage is possible.

The loss of a methyl group bound to silicon to form fragment d (*m/e* 171) and subsequent conversion into fragment e (*m/e* 75) is indicated by a metastable peak at *m/e* 32.9 (calcd $75^2/171 = 32.9$). The sequence a → d → e (Scheme VI) is analogous to one of the processes seen with alkyl silyl ethers (Scheme V). A sequence analogous to the process a → d → e appears to be the major pathway for silyl ethers **32** and **33**, a pathway consistent with the presence of metastable peaks at *m/e* 143.3 (calcd $157^2/172 = 143.3$) and 35.8 (calcd $75^2/157 = 35.8$).

(11) We are indebted to Professor Klaus Biemann and his associates for these measurements.

The mass spectrum of the terminally unsaturated enol ether **18a** exhibited certain distinct differences from the previously discussed spectra. In particular the fragmentation path f → g → h → e (Scheme VII) seems more important for the terminal double-bond isomer; this sequence was indicated by the presence of metastable peaks at *m/e* 90.9 (calcd $130^2/186 = 90.9$), 101.8

SCHEME VII



(calcd $115^2/130 = 101.8$), 43.3 (calcd $75^2/130 = 43.3$), and 49.0 (calcd $75^2/115 = 48.9$). We have no labeling evidence indicating which hydrogen atom is transferred in the fragmentation f → g and suggest the cyclic process (structure f, Scheme VII) as one likely mode of hydrogen transfer. The formation of fragment i (*m/e* 171) is analogous to the previous cases (Scheme V and a → d, Scheme VI). We suspect that peaks in the spectrum of the enol ether **18a** at *m/e* 143 and 73 with a metastable peak at *m/e* 37.3 (calcd $73^2/143 = 37.3$) may result from partial isomerization of the terminal isomer **18a** to one of the internal isomers **19a** or **20a**. Likewise peaks in the spectrum of the internal isomer **20a** at *m/e* 130 and 115 may be the result of partial isomerization to **18a**.

Perhaps the most invariant feature in the mass spectra of all the trimethylsilyl enol ethers is the presence of abundant fragment peaks at *m/e* 75 and 73. Both of these peaks are seen even with the derivatives **9** and **10** of acetophenone and pinacolone where initial fragmentation at allylic bonds (*cf.* Scheme VI) is not feasible.

Experimental Section[12]

Preparation of Starting Materials.—Commercial samples of the starting carbonyl compounds were available except for ketones **21a**, **24**, and **28**. The ketones **21a** and **24** were prepared as previously described.[7] The procedure of Marshall and Fanta[13] was used to prepare 10-methyl-9-hydroxy-2-decalone, mp 122.5–124° (lit.[13] mp 124–125°), and the dehydrated ketone **28**: bp 72–80° (0.15–0.25 mm) [lit.[13] bp 82–83° (0.7 mm)]; ir (CCl_4) 1685 (conjugated C=O) and 1625 cm^{-1} (conjugated C=C); uv (95% EtOH) 239 mμ (ε 17,800) and 309 (70); nmr (CCl_4) δ 5.57 (1 H multiplet, vinyl CH), 0.8–2.9 (12 H multiplet, aliphatic CH), and 1.25 (3 H singlet, CH_3); mass spectrum, molecular ion peak at *m/e* 164 with abundant fragment peaks at *m/e* 136, 121, 91, 79, 77, 41, 39, and 24.

Commercial samples of dimethylformamide and diisopropylamine were purified by redistillation from calcium hydride; 1,2-dimethoxyethane and triethylamine were distilled from $LiAlH_4$ prior to use. Commercial samples of trimethylsilyl chloride were distilled immediately before use. For use in reactions with enolate anions, solutions of the freshly distilled trimethylsilyl chloride in anhydrous 1,2-dimethoxyethane were treated with 0.2–1.0 equiv of anhydrous triethylamine and then filtered through a sintered-glass funnel or centrifuged to remove any residual hydrogen chloride in the form of the insoluble triethylamine hydrochloride. From measurement of nmr spectra of benzene solutions containing triethylamine, trimethylsilyl chloride, and mixtures of these two reagents, we found no evidence for reaction between the amine and the chlorosilane. Commercial halide-free solutions of methyllithium were used after standardization.

Illustrative Procedures for the Preparation of the Trimethylsilyl Enol Ethers. Procedure A.—To a solution of 32.60 g (0.30 mol) of chlorotrimethylsilane and 60.60 g (0.60 mol) of triethylamine in 100 ml of dimethylformamide was added 28.00 g (0.25 mol) of 2-methylcyclohexanone (**21b**). The resulting mixture, from which some pale yellow solid (presumably triethylamine hydrochloride) separated immediately and more separated during the reaction, was refluxed with stirring for 48 hr and then cooled, diluted with 200 ml of pentane, and washed with three 300-ml portions of cold aqueous $NaHCO_3$. The organic layer was combined with the pentane extract from the aqueous washes and washed *rapidly* in succession with portions of cold aqueous 1.5 *M* HCl and cold aqueous $NaHCO_3$. The resulting pentane solution was dried and concentrated to leave 55.5 g of the crude mixture of silyl ethers **22b** and **23b**. Distillation through a short Vigreux column separated 1.878 g of an early fraction, bp 83–90° (20 mm), which contained[14] about 20% of the starting ketone and 36.73 g (80%) of a colorless liquid fraction, bp 90–93° (20 mm), which contained (in order of elution)[14] the starting ketone **21b** (1%), the enol ether **22b** (22%), and the enol ether **23b** (77%). During the course of this reaction, small aliquots were removed and analyzed[14] periodically; after 5 hr the mixture contained **21b** (4%), **22b** (45%), and **23b** (51%) and after 17 hr the composition was **21b** (1%), **22b** (38%), and **23b** (61%).

Fractional distillation of the mixture of enol ethers with a spinning Teflon-band column separated 15.52 g of fractions, bp 94–101° (45 mm), containing various proportions of the enol ethers **22b** and **23b** and 15.31 g of fractions, bp 101–102° (45 mm), $n^{25}D$ 1.4480 [lit.[5f] bp 78–79° (17 mm)], containing[14] the pure higher boiling ether **23b**.

Procedure B.—An ethereal solution conaining 100 mmol of methyllithium was concentrated under reduced pressure and the residual lithium reagent was dissolved in 100 ml of 1,2-dimethoxyethane containing several milligrams of triphenylmethane as an indicator. The resulting solution was cooled to 0° and treated with 10.10 g (100 mmol) of diisopropylamine. To this solution of lithium diisopropylamide was added, dropwise and with stirring over a 10-min period, 2-methylcyclohexanone (**21b**, 11.18 g or 99.8 mmol) until the red color of the triphenylmethide indicator was almost completely discharged. Meanwhile a quenching solution, prepared from 50 ml of 1,2-dimethoxyethane, 5.0 ml (4.4 g or 44 mmol) of triethylamine, and 20 ml (18.4 g or 169 mmol) of chlorotrimethylsilane was centrifuged to remove any of the insoluble triethylamine hydrochloride. By use of a stain-

(12) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 Mc with a Varian Model A-60 nmr spectrometer. The chemical shift values are expressed either in cycles per second or δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a Hitachi–Perkin-Elmer mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates. All reactions involving strong bases or reactive organometallic reagents were performed under a nitrogen atmosphere.

(13) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).

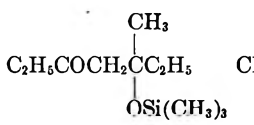
(14) A gas chromatography column packed with Apiezon M suspended on Chromosorb G was employed for this analysis.

less steel cannula, this chlorotrimethylsilane solution was added, rapidly and with stirring, to a cold (0°) solution of the lithium enolate. After the addition was complete, a white solid (LiCl) began to separate after 15 sec. The resulting mixture was stirred at room temperature for 15 min and then partitioned between pentane and cold aqueous $NaHCO_3$. The organic layer was dried and concentrated to leave 49.5 g of residual liquid containing[14] the crude silyl ether **22b**. Fractional distillation through a short Vigreux column separated a 0.70-g forerun [bp 30–59° (7 mm)] and 14.82 g (74%) of the silyl ether **22b** [bp 59–61° (7 mm), $n^{22}D$ 1.4440], which contained[14] less than 2% isomeric silyl ether **23b**.

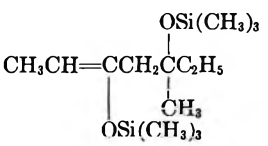
When this procedure employing lithium diisopropylamide was applied to the alkyl methyl ketones **17**, substantial amounts of higher molecular weight products were obtained as a result of competing aldol condensation. In reactions with 2-heptanone (**17a**), this problem was partially overcome by the use of a low reaction temperature (−78 rather than 0°) for the formation of the enolates and subsequent reaction with chlorotrimethylsilane. In this way reaction of 14.60 g (128 mmol) of the ketone **17a** with 190 mmol of lithium diisopropylamide in 1,2-dimethoxyethane followed by reaction with 19.0 g (171 mmol) of chlorotrimethylsilane and 5.0 ml of triethylamine all at −78° afforded, upon distillation, 0.40 g of forerun [bp 102–104° (35 mm)], 16.26 g (65%) of a mixture of silyl ethers [bp 104–106° (35–36 mm), see Table I], and 7.8 g of a residual high-boilng liquid.

The nature of the high-boiling by-products was examined in the reaction of 6.92 g (96.3 mmol) of 2-butanone (**17b**) with 100 mmol of lithium diisopropylamide in 700 ml of bis(β-methoxyethyl) ether.[15] The solution of enolates was treated with a solution of 18.4 g (169 mmol) of chlorotrimethylsilane and 5.0 ml of trimethylamine in 50 ml of bis(β-methoxyethyl) ether. The reaction mixture was distilled to separate 100 ml of distillate, bp 30–155°, which was diluted with pentane and then washed successively with cold, aqueous HCl and with aqueous $NaHCO_3$. Redistillation of the volatile organic products separated a forerun (bp 40–85°), 5.32 g (41% yield) of fractions (bp 85–130°) containing[16] primarily the enol ethers (see Table I), and higher boiling fractions (bp 130–170°) containing[16] mainly bis(β-methoxyethyl) ether.

The less volatile portion of the original reaction mixture was concentrated to remove most of the remaining reaction solvent and the residual material was taken up in pentane and filtered from the insoluble amine hydrochlorides present. After the pentane solution had been washed with aqueous NaCl, dried, and concentrated, distillation separated 6.87 g of fractions of colorless to pale yellow liquid, bp 57–107° (10 mm), which contained[16] various proportions of the reaction solvent and the two aldol derivatives **44** and **45**. A pure sample of the monosilyl ether **44**



44



45

was collected:[16] ir (CCl_4) 1710 cm^{-1} (C=O); uv (95% EtOH) 239 mμ (ε 68) and 284 (32); nmr (CCl_4) δ 0.09 (9 H singlet, $OSiMe_3$), 0.97 (6 H overlapping triplets, $J \sim 7$ cps, CH_3 of two ethyl groups), 1.28 (3 H singlet, (CH_3C), 1.58 (2 H quartet, $J = 7$ cps, CH_2 of one ethyl group), and 2.06–2.68 (4 H multiplet, two CH_2 groups); mass spectrum, no molecular ion, abundant fragment peaks at *m/e* 201, 187, 145, 129, 75, 73, 57, 45, 43, and 29.

Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18. Found: C, 61.19; H, 11.14.

A sample of the more slowly eluted disilyl ether **45** was also collected:[16] ir (CCl_4) 1670 cm^{-1} (enol C=C); uv (95% EtOH) end absorption, ε 2940 at 210 mμ; nmr (CCl_4) δ 0.08 (9 H singlet, $OSiMe_3$), 0.17 (9 H singlet, $OSiMe_3$), 0.85 (2 H triplet, $J =$ 7 cps, CH_3 of ethyl group), 1.20 (3 H singlet, CH_3C), 1.48 (3 H doublet, $J = 6.5$ cps, vinyl CH_3) superimposed on a multiplet in the region 1.10–1.68 (2 H, CH_2 of ethyl group), 2.10 (2 H broad singlet, allylic CH_2), and 4.52 (1 H, quartet, $J = 6.5$ cps, vinyl CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 145, 75, 73, and 45.

Anal. Calcd for $C_{14}H_{32}O_2Si_2$: C, 58.27; H, 11.18. Found: C, 58.45; H, 11.20.

Equilibration of the Trimethylsilyl Enol Ethers. A. 2-Methylcyclohexanone Derivatives.—A mixture of 47.9 mg (0.348 mmol) of triethylamine hydrochloride, 63.3 mg (0.583 mmol) of chlorotrimethylsilane, 548 mg (2.98 mmol) of the enol ether **22b**, a known amount of tetralin (as an internal standard), and 5.0 ml of dimethylformamide was heated to 130° under reflux with stirring for 6 hr and then partitioned between pentane and aqueous $NaHCO_3$. After the organic phase had been dried and concentrated, analysis[14] indicated the following composition (listed in order of elution): **21b** (17% yield), **22b** (13% yield), **23b** (58% yield), and tetralin. Thus, the composition of the enol ether mixture is 18% **22b** and 82% **23b**.

A comparable experiment employing 34.9 mg (0.254 mmol) of triethylamine hydrochloride, 55.6 mg (0.512 mmol) of chlorotrimethylsilane, 624 mg (3.39 mmol) of the isomeric enol ether **23b**, tetralin, and 5.0 ml of dimethylformamide heated to 130° for 4 hr yielded a mixture containing **21b** (16% yield), **22b** (15% yield), **23b** (60% yield), and tetralin. These yields correspond to an enol ether mixture containing 20% **22b** and 80% **23b**.

B. 2-Methylcyclopentanone Derivatives.—The procedure was applied to 36.1 mg (0.264 mmol) of triethylamine hydrochloride, 55.9 mg (0.515 mmol) of chlorotrimethylsilane, 581 mg (3.42 mmol) of the enol ether **23a**, and *n*-butylbenzene (as an internal standard) in 5.0 ml of dimethylformamide. After a 6-hr heating period, the crude product contained (in order of elution)[14] **21a** (16% yield), **22a** (10% yield), **23a** (73% yield), and *n*-butylbenzene corresponding to an enol ether composition of 12% **22a** and 88% **23a**. Similarly, an equilibration experiment starting with 545 mg of the enol ether **22a** gave a mixture containing **21a** (20% yield), **22a** (10% yield), and **23a** (71% yield) corresponding to an enol ether composition of 12% **22a** and 88% **23a**. Additional measurements of these equilibrium compositions gave values in the range 9–11% **22a** and 89–91% **23a**.

C. 2-Methyl-3-pentanone Derivatives.—Three samples (2.2 mmol) of mixtures of enol ethers **31–33**, each containing[17] mainly (>85%) one of the three enol ethers, were added to mixtures of 0.8 mmol of triethylamine hydrochloride, 3.8 mmol of chlorotrimethylsilane, and toluene (an internal standard) in 4.0 ml of dimethylformamide. The mixtures were heated to 130° and aliquots were removed after periods of 14 and 24 hr and subjected to the usual work-up and analysis procedures. Since these isomerizations were significantly slower than the processes described in previous sections, the proportion of ketone **30** in the crude product was greater (37–60%). Each of the mixtures contained (in order of elution)[17] the enol ethers **33**, **32**, and **31**, the internal standard (toluene), and the ketone **30**. After 14 hr the proportions of the enol ether isomers in each reaction mixture remained approximately constant and were within the ranges given: **33**, 6–7%; **32**, 31–35%; and **31**, 59–63%. The average values were 6% **33**, 31% **32**, and 63% **31**.

Absence of Exchange between Enolate Anions and Trimethylsilyl Enol Ethers.—To a solution of 387 mg (2.28 mmol) of the enol ether **5**, a few milligrams of triphenylmethane (as an indicator), and a known amount of durene (as an internal standard) in 2.0 ml of 1,2-dimethoxyethane was added 2.4 ml of a 1,2-dimethoxyethane solution containing 2.30 mmol of methyllithium. The presence of excess methyllithium was indicated by the persistence of the red color of the triphenylmethyl anion. After 5 min a 0.20-ml aliquot of the reaction mixture was removed and partitioned between pentane and aqueous acetic acid. After the organic phase had been dried and concentrated, analysis[14] indicated the presence of cyclohexanone (**3**) (74 and 84% yields in duplicate runs) and the absence of the more slowly eluted ether **5**. The original enolate anion solution was treated with 432 mg (1.92 mmol) of the enol ether **6** and the resulting mixture was stirred for 1.0 hr and subjected to the same isolation and analysis procedure. The crude product contained (in order of elution)[14] **3** (87% yield), durene, **4** (10% yield), and **6** (85% yield). Repetition of this experiment gave comparable results. None of the enol ether **5**, the product expected if exchange of the trimethylsilyl group had occurred, was detected in any case.

(15) A higher boiling solvent was used in this case because the enol ether products had boiling points very similar to 1,2-dimethoxyethane.

(16) A gas chromatography column packed with silicone fluid, no. 710, suspended on Chromosorb P was employed for this analysis.

(17) A gas chromatography column packed with 1,2,3-tris(-(β-cyanoethoxy)propane (TCEP) suspended on Chromosorb P was employed for this analysis.

Interconversions of the Trimethylsilyl Enol Ethers and the Enol Acetates. A. 2-Heptanone Derivatives.—Authentic samples of the enol acetates **41b** and **42b** were prepared as previously described[7] and an authentic sample of the β-diketone **40b** was prepared by the boron trifluoride catalyzed acetylation of 2-heptanone.[18] The pure[16] diketone **40b** was collected from a spinning-Teflon-band column as a colorless liquid: bp 100–101° (20 mm); n^{23}D 1.4460–1.4482 [lit.[18] bp 104–106° (20 mm)]; ir (CCl_4) 1730 (shoulder) and 1705 cm^{-1} (C=O); uv (95% EtOH) 292 mμ (ε 3360); nmr (CCl_4) δ 16.63 (*ca.* 0.3 H singlet, enolic OH), 3.57 (*ca.* 0.7 H triplet, J = 7 cps, COCHCO), 2.07 (6 H, partially resolved singlets, CH_3C of keto and enol forms), 0.7–2.3 (9 H multiplet, aliphatic CH); mass spectrum, molecular ion peak at *m/e* 156 with abundant fragment peaks at *m/e* 100, 71, 58, and 43.

Solutions of 0.70 mmol of methyllithium and several milligrams of bipyridyl (as an indicator)[19] in 0.50 ml of 1,2-dimethoxyethane were treated with slightly less than 1 equiv (see Table V) of one of the silyl ethers **19a** or **20a**. After the solutions had been stirred at 25° for 1 hr, they were diluted with 3.5 ml of 1,2-dimethoxyethane[20] containing known amounts of *n*-dodecane (as an internal standard). Alternatively, enolate anion solutions were prepared by adding about 0.6 mmol (see Table V)

TABLE V

PREPARATION AND ACETYLATION OF ENOLATE ANIONS DERIVED FROM 2-HEPTANONE

Starting material (mmol)	Products, % yield			
	Ketone **17a**	*trans* Acetate **42b**	*cis* Acetate **41b**	Diketone **40b**
cis-Silyl ether **20a** (0.63)	24	2	36	28
trans-Silyl ether **19a** (0.42)	15	74	1	4
cis-Enol acetate **41b** (0.58)	14	0	24	43
trans-Enol acetate **42b** (0.62)	9	72	0	7

of one of the enol acetates **41b** or **42b** to a solution containing 1.4 mmol of methyllithium and several milligrams of bipyridyl[19] in 4.0 ml of 1,2-dimethoxyethane. In all cases, the resulting solutions of enolate anions retained the purple color of the methyllithium–bipyridyl charge-transfer complex indicating the presence of a slight excess of methyllithium.

Each of the enolate anion solutions was added, rapidly and with stirring, to 4.0 ml of acetic anhydride. After the resulting solutions had been stirred for 15 min, they were stirred with a cold (0°) mixture of pentane, water, and excess $NaHCO_3$ until the hydrolysis of acetic anhydride was complete. The pentane layers were dried, concentrated, and analyzed by gas chromatography.[16] With the column used[16] the retention times were, for **17a**, 9.5 min; **42b**, 17.0 min; **41b**, 21.6 min; *n*-dodecane, 26.0 min; and **40b**, 36.0 min. The results of these reactions are summarized in Table V. In each case collected[16] samples of the principal products were identified with authentic samples by comparison of infrared spectra and gas chromatographic retention times.

In a similar experiment, a solution of the lithium enolate from 1.387 g (8.88 mmol) of the *trans*-enol acetate **42b** in 50 ml of 1,2-dimethoxyethane was treated with a solution prepared from 5.06 g (46.7 mmol) of chlorotrimethylsilane, 0.5 ml of triethylamine, and 25 ml of 1,2-dimethoxyethane. The resulting mixture was stirred for 1 hr and then partitioned between pentane and aqueous $NaHCO_3$. After the pentane solution had been washed successively with cold, dilute aqueous HCl and aqueous $NaHCO_3$, it was dried, concentrated, and distilled to separate 0.90 g (48%) of the *trans*-silyl ether **19a**, bp 92° (50–52 mm), $n^{21.5}$D 1.4225, which contained 2–3% lower boiling impurities.

B. Phenylacetone Derivatives.—To obtain authentic samples of the enol acetates **41a** and **42a**, a solution of 26.8 g (0.20 mol) of phenylacetone and 200 g (1.96 mol) of acetic anhydride in 600 ml of carbon tetrachloride was treated with 1.0 ml of aqueous 70% $HClO_4$ and the resulting mixture was stirred for 1.5 hr at 25°. After the reaction mixture had been stirred with a cold (0–5°) mixture of pentane, water, and excess $NaHCO_3$ for 4 hr to hydrolyze the acetic anhydride, the pentane layer was washed with water, dried, concentrated, and fractionally distilled. After separation of 4.71 g of forerun [bp 82–109° (5 mm), n^{25}D 1.5172–1.5280] containing[16] primarily the starting ketone, the mixture of enol acetates (23.7 g or 67%, *ca.* 67% **42a**, and 33% **41a**) was collected at 112–116° (5 mm), n^{25}D 1.5312–1.5328 [lit.[21] bp 67–69° (0.8 mm), n^{25}D 1.5320, stereochemistry unspecified]. Samples of each of the pure enol acetates were collected from the gas chromatograph.[16] The more rapidly eluted *trans* acetate **42a** was separated as a colorless liquid: ir (CCl_4) 1765 (enol ester C=O) and 1685 cm^{-1} (enol C=C); uv (95% EtOH) 248.5 mμ (ε 18,000) and 325 sh (415); nmr (CCl_4) δ 6.9–7.3 (5 H multiplet, aryl CH), 5.80 (1 H doublet, J = 1.1 cps, vinyl CH), 2.08 (3 H singlet, $OCOCH_3$), and 2.01 (3 H partially resolved doublet, vinyl CH_3); mass spectrum, molecular ion peak at *m/e* 176 with abundant fragment peaks at *m/e* 134, 91, 45, 43, and 39.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.93; H, 6.93.

The more slowly eluted[16] *cis* isomer **41a** was also collected as a colorless liquid: ir (CCl_4) 1765 (enol ester C=O) and 1685 cm^{-1} (enol C=C); uv (95% EtOH) 242.5 mμ (ε 15,200) and 324 sh (253); nmr (CCl_4) δ 7.2 (5 H partially resolved multiplet, aryl CH), 6.15 (1 H broad singlet, vinyl CH), 2.07 (3 H singlet, $OCOCH_3$), and 2.04 (3 H partially resolved doublet, vinyl CH_3); mass spectrum, molecular ion peak at *m/e* 176 with abundant fragment peaks at *m/e* 134, 91, 45, 43, and 39.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.18; H, 6.94.

Samples of the silyl ethers (181–196 mg or 0.88–0.95 mmol of a mixture of 85% **16** and 15% **15**) were added to solutions of 1.0 mmol of methyllithium and several milligrams of bipyridyl (as an indicator)[19] and known weights of 1,3,5-triisopropylbenzene (internal standard) in 10 ml of 1,2-dimethoxyethane. After the resulting purple solutions (excess methyllithium present) had been stirred for 15–20 min, 1.0-ml aliquots were removed and quenched in an equal volume of acetic anhydride. After the usual isolation procedure, the crude neutral product was analyzed by gas chromatography,[16,22] the retention times[16] being, for **14**, 24.5 min; 1,3,5-triisopropylbenzene, 34.0 min; **42a**, 51.6 min; and **41a**, 56.4 min. The mixtures contained the ketone **14** (6–18% yield) and the enol acetates (68–78% yield) having a composition of 20% **42a** and 80% **41a**. When a 1.0-ml sample of oxygen gas was added to the atmosphere above the enolate solution, and the resulting solution was stirred for 5 min, the product contained the ketone **14** (19% yield) and the enol acetates (65% yield) having a composition 38% **42a** and 62% **41a**. Thus, the presence of oxygen can catalyze the interconversion of stereoisomeric enolate anions as has been noted elsewhere.[23] The corresponding reaction employing 802 mg (3.9 mmol) of the *trans*-silyl ether **15** and 4.0 mmol of methyllithium in 2.0 ml of 1,2-dimethoxyethane gave a crude product containing[16,22] the ketone **14** (5% yield) and the enol acetates (95% yield, 99% of **42a** and 1% of **41a**). From each of these reactions, collected[16] samples of the principal products were identified with authentic samples by comparison of infrared spectra and gas chromatographic retention times. From the reaction with the *trans*-silyl ether **15** none of the β-diketone **40a** was detected;[22] from the *cis* isomer **16** a small peak (less than 2% of the reaction product) was present which had a retention time[22] corresponding to the β-diketone **40a**. With the column used for this analysis,[22] the retention times were, for 1,3,5-triisopropylbenzene, 8.2 min; **14**, 16.0 min; **41a** and **42a** (not resolved), 24.4 min; and **40a**, 27.6 min. An authentic sample of this β-diketone **40a** was prepared by the acetylation of phenylacetone in the presence of boron

(18) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 132 (1954).

(19) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(20) The reaction of 1 *M* solutions of trimethylsilyl enol ethers with 1 *M* solutions of methyllithium in 1,2-dimethoxyethane requires 5–15 min for completion. It is advantageous to carry out this bimolecular reaction in relatively concentrated solution, and then to add additional solvent if a more dilute solution is desired.

(21) G. G. Smith, *J. Amer. Chem. Soc.*, **75**, 1134 (1953).

(22) A gas chromatography column packed with silicone gum, XE-60, suspended on Chromosorb P was employed for this analysis.

(23) Unpublished work by Professor G. W. Whitesides and E. J. Panek, Department of Chemistry, Massachusetts Institute of Technology.

trifluoride.[18] The product separated from petroleum ether (bp 30–60°) at Dry Ice temperature as white prisms: mp 56.5–57.5° (lit.[18] mp 58.5–59.5°); ir (CCl_4) 1615 and 1410 cm^{-1} (very broad, enolic β-diketone); uv (95% EtOH) 222 mμ (shoulder, ε 6050) and 286 (10,300); nmr (CCl_4) δ 16.95 (1 H singlet, enol OH), 7.0–7.5 (5 H multiplet, aryl CH), 1.82 (6 H singlet, CH_3C); mass spectrum, molecular ion peak at *m/e* 176 with abundant fragment peaks at *m/e* 161, 134, 115, 77, 55, and 43.

A mixture of 66.8 g (0.50 mol) of phenylacetone, 20 g (0.88 mol) of sodium hydride (prewashed with pentane), and 400 ml of 1,2-dimethoxyethane was stirred for 3.2 hr and then allowed to stand for 14 hr. The supernatant liquid was transferred under nitrogen to a separate vessel; acid–base titration of an aliquot of this solution indicated the total base concentration to be 1.00 *M*. When a 1.0-ml aliquot of the solution was mixed with 1,3,5-triisopropylbenzene (an internal standard), quenched in aqueous NH_4Cl, and then analyzed,[16] the calculated yield of phenylacetone indicated that the solution was 0.96 *M* in phenylacetone enolate. In the 6-μ region of the infrared the solution shows peaks at 1599 (shoulder), 1575 (strong), and 1550 (strong). The nmr spectrum has a 5 H multiplet at δ 6.3–7.5 (aryl CH), a 1 H singlet at δ 4.70 (enolate vinyl CH), and a 3 H singlet at 1.83 (CH_3C). Aliquots of this sodium enolate solution were also quenched as previously described in acetic anhydride and in a solution of excess chlorotrimethylsilane in 1,2-dimethoxyethane. From reaction with acetic anhydride, the crude product contained[16] the ketone **14** (5% yield) and the enol acetates (91% yield, 99% **42a**, and 1% **41a**). Similarly, from reaction with the chlorosilane with naphthalene added as an internal standard, the crude product contained the ketone **14** (9% yield) and the silyl enol ethers (90% yield, 96% **15**, and 4% **16**). Consequently, this sodium enolate solution contains predominantly the *trans* enolate stereoisomer.

C. 2-Butanone Derivatives.—An authentic sample of the diketone **40c**, prepared by the reaction of methyl iodide with acetylacetone in the presence of K_2CO_3 and acetone, was isolated as a colorless liquid, bp 30–60° (100 mm), $n^{25}D$ 1.4412 [lit.[24a] bp 170–172° (760 mm)] with nmr absorption corresponding to the published spectrum:[24b] ir (CCl_4) 1730 (shoulder), 1705, and 1610 cm^{-1} (broad, keto and enol form of β-diketone); uv (95% EtOH) 290 mμ (ε 3350); mass spectrum, molecular ion peak at *m/e* 114 with abundant fragment peaks at *m/e* 99, 71, and 43. Application of the previously described reaction and isolation procedures to a solution of 36.0 g (0.50 mol) of 2-butanone, 153.0 g (1.50 mol) of acetic anhydride, and 1.6 g of aqueous 70% $HClO_4$, in 400 ml of carbon tetrachloride yielded, after fractional distillation, 16.67 g (25%) of a colorless liquid fraction, bp 93–130° (760 mm), $n^{25}D$ 1.4223, which contained[16,25] small amounts of carbon tetrachloride and 2-butanone and a mixture of enol acetates (79% of **42c**, eluted first, and 21% **41c**, eluted second).[26] Samples of each enol acetate were collected.[25] The *trans* isomer **42c** has the following spectral properties: ir (CCl_4) 1760 (enol ester C=O) and 1705 cm^{-1} (enol C=C); uv (95% EtOH) end absorption with ε 963 at 210 mμ; nmr (CCl_4) δ 4.97 (1 H quartet with additional small splitting not resolved, *J* = 6.4 cps, vinyl CH), 2.07 (3 H singlet, $OCOCH_3$), 1.80 (3 H quintet, both *J* values about 1.3 cps, α-CH_3C), 1.48 (3 H, doublet of quartets, *J* = 6.4 and 1.3 cps, β-CH_3C); mass spectrum, molecular ion peak at *m/e* 114 with abundant fragment peaks at *m/e* 72, 71, 57, and 43. Since the nmr spectrum of this sample lacks appreciable absorption at δ 4.65 (vinyl CH) which is present in the spectrum of a mixture[26] containing the terminal enol acetate

$$CH_3CH_2C(=CH_2)OCOCH_3$$

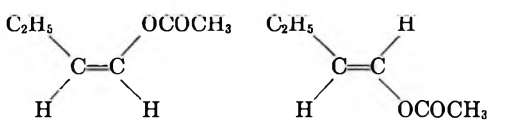
40

isomer **46**, we conclude that our sample of enol acetate **42c** contains less than 5% isomer **46**.

The *cis* isomer **41c** was also a colorless liquid: ir (CCl_4) 1765, 1748 (enol ester C=O, presumably split by Fermi resonance with the overtone of a peak at 890 cm^{-1}), and 1690 cm^{-1} (enol C=C); uv (95% EtOH) end absorption with ε 1200 at 210 mμ; nmr (CCl_4) δ 5.10 (1 H quartet, *J* = 7.0 cps, vinyl CH), 1.97 (3 H singlet, $OCOCH_3$), 1.78 (3 H quintet, both *J* values about 1.0 cps, α-CH_3C), and 1.60 (3 H doublet of quartets, *J* = 7.0 and 1.0 cps, β-CH_3C); mass spectrum, molecular ion peak at *m/e* 114 with abundant fragment peaks at *m/e* 72, 71, 57, and 43. As noted previously,[7] the chemical shift difference for the vinyl protons of the enol acetates (in CCl_4, δ 4.97 for the *trans* isomer **42c** and δ 5.10 for the *cis* isomer **41c**) was increased by measuring the spectra in benzene-d_6 where the chemical shift values were δ 4.86 for **42c** and 5.13 for **41c**. These observations are consistent with the stereochemical assignments given.[7,26]

Following previously described procedures, an enolate solution was prepared by reaction for 1.0 hr of 80.1 mg (0.56 mmol) of the silyl enol ethers (92% **19b** and 8% **20b**) with 1.5 mmol of methyllithium in 1.5 ml of 1,2-dimethoxyethane containing tetralin (an internal standard) and several milligrams of triphenylmethane. After reaction with acetic anhydride and the usual isolation procedure, the product was analyzed on a column[25] which gave the following retention times: **42c**, 16.5 min; **41c**, 19.5 min; **40c**, 37.0 min; and tetralin, 48.7 min. The crude product contained[25] the *trans* acetate **42c** (51% yield), the *cis* acetate **41c** (2% yield), and the diketone **40c** (9% yield). The corresponding reaction with 114.5 mg (0.79 mmol) of a silyl ether sample which contained 97% *cis* isomer **20b** and 3% *trans* isomer **19b** yielded a crude product containing[25] the *trans* acetate **42c** (5% yield), the *cis* acetate **41c** (16% yield), the diketone **40c** (32% yield), and several minor unidentified higher boiling materials. Collected[25] samples of each of the principal products from these reactions were identified with authentic samples by comparison of infrared spectra and gas chromatographic retention times.

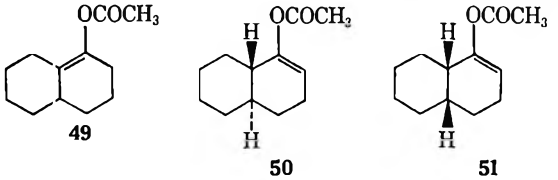
D. Butyraldehyde Derivatives.—Authentic samples of the enol acetates **47** and **48** were available from other studies.[23] An enolate solution was generated by reaction for 45 min of 535 mg (3.71 mmol) of the silyl ether **13** with 3.73 mmol of methyllithium in 10 ml of 1,2-dimethoxyethane containing *n*-decane (an internal standard) and several milligrams of triphenylmethane (as an indicator). After reaction with acetic anhydride, the crude product was isolated in the usual way and analyzed with a column[16] which gave the following retention times: **47**, 20.1 min; **48**, 25.2 min; and *n*-decane, 49.2 min. The crude



47 **48**

product contained[16] the unchanged silyl ether **13** (2% recovery) and the acetate **48** (90% yield). From the corresponding reaction with 526 mg (3.65 mmol) of the silyl ether **12**, the crude product contained[16] the unchanged silyl ether **12** (8% recovery) and the acetate **47** (92% yield). Collected[16] samples of the products were identified with authentic samples by comparison of infrared spectra and gas chromatographic retention times.

E. 1-Decalone Derivatives.—Authentic samples of the enol acetates **49–51** were available from earlier studies.[7] After reac-



49 **50** **51**

tion of a solution of 79.0 mg (0.35 mmol) of a silyl enol ether mixture (77% **25**, 20% **26**, and 3% **27**) with 1.0 mmol of methyllithium in 1.0 ml of 1,2-dimethoxyethane for 1 hr, the reaction mixture (also containing tetralin and triphenylmethane) was quenched in acetic anhydride and subjected to the usual isolation process. With the column[25] used retention times were as follows: tetralin, 18.2 min; **24**, 43.5 min; **49**, 65.0 min; **50**, 77.5 min; **51**, 84.9 min; and a product believed to be 2-acetyl-1-

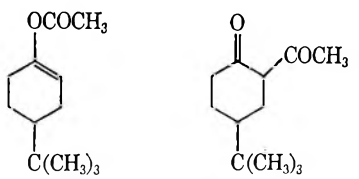
(24) (a) A. W. Johnson, E. Markham, R. Price, and K. B. Shaw *J. Chem. Soc.*, 4254 (1958); (b) J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 2105 (1964).

(25) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed for this separation.

(26) W. E. Parham and J. F. Dooley [*J. Org. Chem.*, **33**, 1476 (1968)] have reported the acid-catalyzed reaction of 2-butanone with isopropenyl acetate to give the expected (see ref 7) mixture of enol acetates, **41c**, **42c**, and **46**, bp 110–120° (760 mm), $n^{26}D$ 1.4065. Since neither we nor the previous workers were able to resolve the more rapidly eluted *trans* isomer **42c** and the terminal double-bond isomer **46** on the columns employed, we used the alternative preparative route to enol acetates to minimize the amount of the less stable isomer **46** present in the product mixture.

decalone, 150.9 min. The crude product contained **24** (6% yield), **49** (2% yield), **50** (44% yield), **51** (15% yield), and several higher boiling components. The corresponding reaction with 68.8 mg (0.31 mmol) of a silyl enol ether mixture (36% **25**, 59% **26**, and 5% **27**) yielded a crude product containing **24** (3% yield), **49** (7% yield), **50** (18% yield), **51** (32% yield), and several higher boiling peaks. Collected[25] samples of the enol acetate products were identified with authentic samples by comparison of infrared spectra and gas chromatographic retention times. The results of these transformations allow us to conclude that isomers **25** and **50** are stereochemically related as are **26** and **51**.

F. 4-*t*-Butylcyclohexanone Derivatives.—An authentic sample of the enol acetate **52** was available from previous studies.[27]



52 **53**

After reaction of 18.6 g (89.8 mmol) of the pyrrolidine enamine[27] of 4-*t*-butylcyclohexanone with 20.7 g (203 mmol) of acetic anhydride in 50 ml of dioxane at 25° for 24 hr, the solution was diluted with 10 ml of water, refluxed for 30 min, and concentrated. The residual liquid was partitioned between pentane and water, and the resulting organic phase was washed with aqueous NaCl, dried over Na_2SO_4, concentrated, and distilled in a short-path still (1.0–1.1 mm and 105–132° bath). The crude distillate (14.72 g of pale yellow oil, $n^{26}D$ 1.4942) was fractionally distilled to separate 7.93 g (45%) of the **diketone 53** as a colorless liquid: bp 99–100° (0.9–1.0 mm); $n^{26}D$ 1.4956; ir (CCl_4) 1610 cm^{-1} (broad, enolic β-diketone); uv (95% EtOH) 290 mμ (ε 9840); nmr (CCl_4) δ 1.1–2.6 (*ca.* 7 H multiplet, aliphatic CH), 2.08 (3 H singlet, vinylic or acetyl CH_3), and 0.93 [9 H singlet, $(CH_3)_3C$]; mass spectrum, molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 181, 139, 125, 57, 55, 43, and 41.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.14; H, 10.13.

After reaction for 1 hr of 2.7 mmol of methyllithium with 584.7 mg (2.58 mmol) of the silyl ether **6** in 10 ml of 1,2-dimethoxyethane containing several milligrams of triphenylmethane, the enolate solution was treated with *n*-tetradecane (as an internal standard) and quenched in acetic anhydride. Following the usual isolation procedure, the crude product was analyzed on a column[14] on which the retention times were, for **4**, 9.4 min; **52**, 22.2 min; *n*-tetradecane, 30.7 min; and **53**, 47.0 min. The crude product contained **4** (12% yield), **52** (63% yield), and **53** (12% yield). Collected[14] samples of the enol acetate **52**, and the diketone **53** were identified with authentic samples by comparison of infrared spectra and gas chromatographic retention times.

Registry No.—**5**, 6651-36-1; **6**, 19980-19-9; **9**, 13735-81-4; **10**, 17510-46-2; **12**, 19980-22-4; **13**, 19980-23-5; **15**, 19980-24-6; **16**, 19980-25-7; **18a**, 19980-26-8; **18b**, 6651-40-7; **19a**, 19980-27-9; **19b**, 19980-29-1; **20a**, 19980-30-4; **20b**, 19980-31-5; **22a**, 19980-32-6; **22b**, 19980-33-7; **23a**, 19980-34-8; **23b**, 19980-35-9; **25**, 19980-36-0; **26**, 19980-37-1; **27**, 19980-38-2; **29**, 19980-39-3; **31**, 19980-40-6; **32**, 19980-41-7; **33**, 19980-42-8; **35**, 19980-43-9; **41a**, 19980-44-0; **41c**, 15984-02-8; **42a**, 19980-46-2; **42c**, 15984-03-9; **44**, 19980-48-4; **45**, 19980-49-5; **53**, 19980-50-8.

(27) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).

β-Keto Sulfoxides. IV. Conversion into β-Keto Sulfides, Vinyl Ethers, and Enol Acetates[1]

GLEN A. RUSSELL AND EDWARD T. SABOURIN

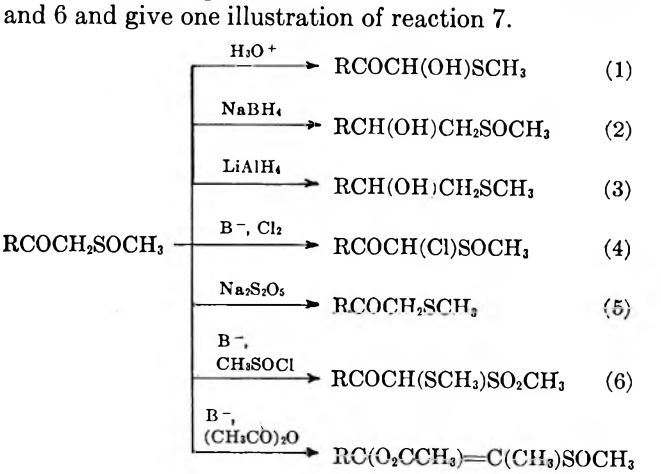
Department of Chemistry, Iowa State University, Ames, Iowa 50010

Received April 2, 1968

β-Keto sulfoxides are reduced with sodium metabisulfite to β-keto sulfides. Alkylation of the β-keto sulfide followed by reduction, O methylation, and base-catalyzed elimination in dimethyl sulfoxide solution yields the enol ether. Acylation of the keto sulfides by sodium hydride followed by acetic anhydride gives the enol acetate. Similar treatment of β-keto sulfoxides yields either the enol acetate or the α-acetoxy β-keto sulfide. Reaction of the salt of a β-keto sulfoxide with methanesulfinyl chloride yields a sulfone sulfide rather than the expected disulfoxide. A sulfone sulfide is also produced from the reaction of the enolate anion of acetylacetone or dibenzoylmethane with two molecules of methanesulfinyl chloride. The formation of the sulfone sulfide is pictured as a base-catalyzed modification of the Pummerer reaction.

This paper reports some of our continuing studies of the synthetic utility of β-keto sulfoxides. Such β-keto sulfoxides can be readily prepared by the condensation of esters with the methylsulfinyl carbanion ($CH_3SOCH_2^-$).[2,3] β-Keto sulfoxides will undergo monoalkylation reactions in basic solution.[4,5] In addition a variety of other products still containing one sulfur atom can be formed from the β-keto sulfoxides.[6] We have already described the conversions illustrated in reactions 1–4.[2,4,6] In the present work we describe reactions 5 and 6 and give one illustration of reaction 7.

$$RCO_2R' + CH_3SCOH_2^- \longrightarrow RCOCH_2SOCH_3 \xrightarrow[CH_3I]{B^-} RCOCH(CH_3)SOCH_3$$



(1) This work was supported by the Army Office of Research (Durham). For part III, see G. A. Russell and G. J. Mikol, *J. Amer. Chem. Soc.*, **88**, 5498 (1966).

(2) H.-D. Becker, G. J. Mikol, and G. A. Russell, *ibid.*, **85**, 3410 (1963).

(3) E. J. Corey and M. J. Chaykovsky, *ibid.*, **86**, 1639 (1964); 1345 (1965).

(4) G. A. Russell and G. J. Mikol, *ibid.*, **88**, 5498 (1966).

(5) P. G. Gassman and G. O. Richmond, *J. Org. Chem.*, **31**, 2355 (1966).

(6) G. A. Russell, E. Sabourin, and G. J. Mikol, *ibid.*, **31**, 2854 (1966).

We had previously attempted to prepare vinyl ethers from β-hydroxy sulfoxides.[4] However, basic or thermal elimination reaction of β-methoxy sulfoxides yielded the vinyl sulfoxides or the ketone (Scheme I).

Scheme I

$$RCH(OH)CH_2SOCH_3 \xrightarrow[CH_3I]{B^-}$$

$$RCH(OCH_3)CH_2SOCH_3 \begin{cases} \xrightarrow{B^-} RCH{=}CHSOCH_3 + CH_3OH \\ \xrightarrow{\Delta} RCOCH_3 + CH_3SOH \end{cases}$$

We now have found that the base-catalyzed elimination of β-methoxy sulfides in dimethyl sulfoxide (DMSO) solution yields the vinyl ether. Since the β-keto sulfide can be mono- or dialkylated, a variety of vinyl ethers can be readily prepared from the β-keto sulfide after reduction and etherification.

Results and Discussion

Selective reduction of the sulfoxide group of ω-(methylsulfinyl)acetophenone was achieved by the use of sodium metabisulfite ($Na_2S_2O_5$) in aqueous solution at 90° for 20 hr.[7] In Table I some typical yields of sulfides are given. The reaction is clean and no impurities were detected in the crude products by proton magnetic resonance (pmr).

Table I
Sodium Metabisulfite Reductions[a]

Substrate	Product	% yield
$C_6H_5COCH_2SOCH_3$	$C_6H_5COCH_2SCH_3$	52
$C_6H_5CH(OH)CH_2SOCH_3$	$C_6H_5CH(OH)CH_2SCH_3$	93
$C_6H_5CH(OCH_3)CH_2SOCH_3$	$C_6H_5CH(OCH_3)CH_2SCH_3$	80
$C_6H_5CH{=}CHSOCH_3$	$C_6H_5CH{=}CHSCH_3$	66
$C_6H_5CH(O_2CCH_3)CH_2SOCH_3$	$C_6H_5CH(O_2CCH_3)CH_2SCH_3$	89

[a] Sodium metabisulfite (10 g) in 25 ml of water/g of sulfoxide, 20 hr at 90°.

The β-methoxy sulfides (**1**) of Table II were prepared from the β-keto sulfides by reduction with sodium borohydride followed by methylation of the sodium salt

Table II
Preparation of Enol Ethers by Base-Catalyzed Elimination of 1

	Substituents				Yield, %	
Compd	R_1	R_2	R_3	R_4	2	3
1a	C_6H_5	H	H	CH_3	56	16
1b	C_6H_5	CH_3	H	CH_3	43	Nil
1c	C_6H_5	CH_3	CH_3	CH_3	Nil	...
1d	C_6H_5	H	H	C_6H_5	49	15
1e	C_6H_5	CH_3	H	C_6H_5	64	Nil
1f	C_6H_5	CH_3	CH_3	C_6H_5	82	...

of the β-hydroxy sulfide by methyl iodide in tetrahydrofuran (THF) solution. The major elimination product of the β-methoxy sulfides were the vinyl ethers (**2**) accompanied by small amounts of the vinyl sulfides (**3**) when $R_2 = R_3 = H$.

(7) Thianthrone sulfoxide has been selectively reduced by sodium borohydride–sodium hydroxide [A. L. Ternay, Jr., and P. W. Chaser, *J. Org. Chem.*, **32**, 3814 (1967)]. The sodium metabisulfite reduction of methionine sulfoxide has been reported [F. Michael and H. Schmitz, *Chem. Ber.*, **72**, 992 (1939)].

$$\underset{\mathbf{1}}{R_1CH(OCH_3)CR_2R_3SR_4} \xrightarrow[70\text{–}75^\circ]{t\text{-BuOK/DMSO}}$$

$$\underset{\mathbf{2}}{R_1C(OCH_3){=}CR_2R_3} + \underset{\mathbf{3}}{R_1CH{=}CR_2SR_4}$$

Another reaction of the β-keto sulfide that we investigated was the conversion into the enol acetate (reaction 8) **4**.[8] Attempts to prepare **4** from the vinyl sulfoxide (**5**) (readily available by the oxidation of the sulfide **3a**

$$C_6H_5COCH_2SCH_3 \xrightarrow[2.\ (CH_3CO)_2O]{1.\ NaH,\ THF}$$

$$\underset{\mathbf{4}}{C_6H_5C(O_2CCH_3){=}CHSCH_3} \quad (8)$$

with sodium periodate[6]) led to the normal Pummerer rearrangement product, **6**. We had expected that **4** might be a product by analogy with the formation of **7** from **5** and thionyl chloride (Scheme II).[6]

Scheme II

$$\underset{\mathbf{5}}{C_6H_5CH{=}CHSOCH_3} \begin{cases} \xrightarrow{(CH_3CO)_2O} \mathbf{4} \\ \xrightarrow{(CH_3CO)_2O} \underset{\mathbf{6}}{C_6H_5CH{=}CHSCH_2(O_2CCH_3)} \\ \xrightarrow{SOCl_2} \underset{\mathbf{7}}{C_6H_5C(Cl){=}CHSCH_3} \end{cases}$$

When the salt of a β-keto sulfoxide is treated with acetic anhydride either a Pummerer-type rearrangement (reaction 9) or O acylation (reaction 10) occurs.

$$RCOCH_2SOCH_3 \xrightarrow[2.\ (CH_3CO)_2O]{1.\ NaH,\ THF} RCOCH(O_2CCH_3)SCH_3 \quad (9)$$

8a, R = phenyl
b, R = cyclohexyl

$$C_6H_5COCH(CH_3)SOCH_3 \xrightarrow[2.\ (CH_3CO)_2O]{1.\ NaH,\ THF}$$

$$\underset{\mathbf{9}}{C_6H_5C(O_2CCH_3){=}C(CH_3)SOCH_3} \quad (10)$$

a and intermediate **10** (Scheme III).[9] Apparently

Scheme III

$$RCOCH_2SOCH_3 \begin{cases} \xrightarrow[path\ a]{(CH_3CO)_2O} [RCOCH_2S(O_2CCH_3)CH_3]^+ \xrightarrow{-H^+} \\ \xrightarrow[path\ b]{NaH,\ THF} RCOCHSOCH_3 \xrightarrow{(CH_3CO)_2O} \end{cases} \underset{\mathbf{10}}{[RCOCHS^+(O_2CCH_3)CH_3][CH_3CO_2^-]} \longrightarrow \mathbf{8}$$

The classical Pummerer rearrangement occurs *via* path intermediate **10** can be formed by path b as well. Path b represents a base-catalyzed analog Pummerer reaction. Since monoalkylated β-keto sulfoxides are not prone to undergo the Pummerer reaction[2,4] the formation of **8** and **9** from the respective β-keto sulfoxides can be rationalized.

Methanesulfinyl chloride was found to react with β-keto sulfoxides in a manner similar to acetic anhydride or acetyl chloride.[10] In the absence of base the

(8) β-Keto sulfones also give O acylation [N. M. Carroll and W. I. O'Sullivan, *J. Org. Chem.*, **30**, 2830 (1965).

(9) G. A. Russell and G. J. Mikol, "Mechanisms of Molecular Migrations," B. S. Thyagarajan, Ed., Vol. I, Interscience Publishers, New York, N.Y., 1968, p 157.

(10) F. G. Bordwell and B. M. Pitts, *J. Amer. Chem. Soc.*, **77**, 574 (1955).

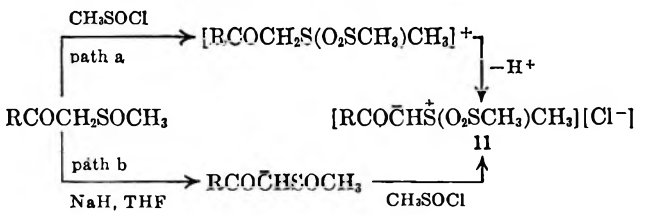
α-chloro-β-keto sulfide (reaction 11) resulted, while the reaction in the presence of base yielded the sulfonyl fulfide (reaction 12). It seems reasonable that the

$$C_6H_5COCH_2SOCH_3 + CH_3SOCl \longrightarrow C_6H_5COCH(Cl)SCH_3 \quad (11)$$

$$C_6H_5COCH_2SOCH_3 \xrightarrow[2.\ CH_3SOCl]{1.\ NaH,\ THF} C_6H_5COCH(SO_2CH_3)SCH_3 \quad (12)$$

products of reactions 11 and 12 could result from the common intermediate shown in Scheme IV. In the

SCHEME IV



absence of base, intermediate **11** yields the products of reaction 11 *via* process 11a. In the presence of base the process 12a would occur.

$$11 \xrightarrow{H^+} CH_3SO_2H + [RCOCH{=}SCH_3]^+Cl^- \longrightarrow RCOCH(Cl)SCH_3 \quad (11a)$$

$$11 \longrightarrow CH_3SO_2^- + Cl^- + [RCOCH{=}SCH_3]^+ \longrightarrow RCOCH(O_2SCH_3)SCH_3 \quad (12a)$$

The observation of reaction 12 explains a surprising result that we had observed previously. Compound **12** is a potential precursor for a 1,2,3 triketone.[11] Al-

$$\underset{12}{(RCO)_2CHSOCH_3} \xrightarrow{H^+} RCOCOCOR + CH_3SH$$

though methanesulfonyl chloride reacts readily with the anion of a β diketone to yield a diacyl(methylsulfonyl)-methane,[12] the reaction of methanesulfinyl chloride with the enolate anion of 2,4-pentanedione or bibenzoylmethane led to the sulfonyl sulfides, **13a** and **13b**. The reaction appears to be analogous to reaction 12 and involves a Pummerer-type reaction of intermediate **12**.[12a]

$$(RCO)_3CH^- + CH_3SOCl \longrightarrow (RCO)_2CHSOCH_3 \longrightarrow [(RCO)_2CSOCH_3]^- \xrightarrow{CH_3SOCl} (RCO_2)C(O_2SCH_3)SCH_3$$

13a, R = CH_3
b, R = C_6H_5

Experimental Section

Sodium Metabisulfite Reduction.—The reactants were dissolved in water and heated to approximately 90° with stirring for 24 hr. For every gram of sulfoxide to be reduced, 10 g of sodium metabisulfite and 25 ml of water were used. At the end of the reaction period the mixture was cooled and extracted thoroughly with ether. The extracts were dried over magnesium sulfate and filtered. Removal of the solvent gave the sulfide, usually in a high state of purity. The infrared (ir) and pmr spectra of the reduction products were identical with those of materials previously produced by independent synthesis.[6]

Preparation of β-Methoxy Sulfides.—The analogous β-hydroxy sulfides were O methylated using sodium hydride and methyl iodide in THF as previously described.[6] The β-hydroxy sulfides were prepared from β-keto sulfoxides and sulfides by alkylation,[4,6] followed by either lithium aluminum hydride reduction for sulfoxides[4,6] or sodium borohydride reduction for sulfides.[6] The crude β-methoxy sulfides were allowed to react without extensive purification.

Preparation of Enol Ethers.—The β-methoxy sulfide in DMSO solution (*ca.* 1 g/5 ml) was placed in a flask equipped with a magnetic stirrer, reflux condenser, and nitrogen inlet and outlet. An excess of potassium *t*-butoxide was added and the temperature raised to 70–75°. The reaction time for phenyl sulfides was 5 hr. For methyl sulfides reaction times of 12–24 hr were required. After reaction the mixture was cooled and poured into ice water. After extraction with ether, the extracts were washed with water and dried over magnesium sulfate. Removal of the solvent gave the crude product from which the enol ether was distilled. The pot residue was chromatographed on silica gel to obtain the unsaturated sulfide if the pmr of the crude product indicated its presence.

α-Methoxystyrene (2a–d) had bp 50–51° (2 mm) [lit.[13] bp 30–32° (0.4 mm)]. The spectra of **3a** were identical with those of material produced by the sodium metabisulfite reduction of ω-(methylsulfinyl)styrene.[6]

α-Methoxy-β-methylstyrene (2b–e) had bp 56–57° (2 mm) [lit.[14] bp 96–98° (19 mm)]. The spectra were consistent with a mixture of *cis* and *trans* isomers: pmr (CCl_4) δ 1.67 and 1.74 (doublets, 3 total, J = 7 Hz), 3.45 and 3.54 (singlets, 3 total), 4.69 and 5.22 (quartets, total 1), 7.0–7.5 (m, 5).

β-(Phenylmercapto)styrene (3d) was identified by oxidation to the known sulfone, mp 73–74° [lit.[15] mp 74.0–74.5°].

α-Methoxy-β,β-dimethylstyrene (2f) had bp 59–60° (2 mm); ir (CCl_4) 1661 cm^{-1} (C=C); pmr (CCl_4) δ 1.60 (s, 3), 1.79 (s, 3), 3.20 (s, 3), 7.21 (s, 3); mass spectrum (70 eV), molecular ion at *m/e* 162.

The enol ethers hydrolyzed in the presence of aqueous acid to the corresponding ketones.

α-Acetoxy-β-(methylmercapto)styrene (4).—ω-(Methylmercapto)acetophenone[6] (4.15 g, 25 mmol), in 100 ml of THF was added to a well-stirred slurry of 0.60 g of sodium hydride (25 mmol) in 50 ml of THF. After the evolution of hydrogen had ceased, 2.55 g (25 mmol) of acetic anhydride was added dropwise and the mixture was stirred at room temperature for 2 hr, quenched with water, and extracted with chloroform. After the extracts were dried over sodium sulfate, the solvent was removed to give 4.92 g (92%) of **4**: mp 55–56°; ir (CCl_4) 1767 (C=O), 1190 cm^{-1} (C—O); pmr δ 2.23 (s, 3), 2.30 (s, 3), 6.31 (s, 1), 7.26 (s, 5).

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.81; S, 15.37. Found: C, 63.62; H, 5.82; S, 15.35.

Acetoxymethyl β-Styryl Sulfide (6).—A solution of β-(methylsulfinyl)styrene (**5**, 4.15 g, 25 mmol) in 20 ml of acetic anhydride was heated on a steam bath for 12 hr. The mixture was cooled and added cautiously to a saturated solution of sodium bicarbonate. When the reaction had ceased, the mixture was extracted with chloroform. The extracts were dried over magnesium sulfate. Removal of the solvent distillation under reduced pressure gave **6** (4.78 g, 92%) as a colorless liquid: bp 94–95° (0.08 mm); ir (CCl_4) 1751 (C=O), 1192 cm^{-1} (C—O); pmr δ 1.98 (s, 3), 5.22 (s, 2), 6.53 and 6.77 (AB quartet, 2, J = 15.5 Hz), 7.18 (s, 5).

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.81; S, 15.37. Found: C, 63.40; H, 5.84; S, 15.38.

Reaction of Acetic Anhydride with Salts of β-Keto Sulfoxides.—ω-(Methylsulfinyl)acetophenone (9.1 g, 50 mmol) was subjected to the action of 1.2 g of sodium hydride (50 mmol) and 5.1 g of acetic anhydride (50 mmol) according to the procedure employed in the preparation of **4**. Distillation of the isolated product yielded 8.35 g (75%) of **ω-acetoxy-ω-(methylmercapto)acetophenone** (**8a**), bp 98–100° (0.1 mm). The product had identical spectral properties with those of **8a** prepared by the Pummerer rearrangement of ω-(methylsulfinyl)acetophenone by acetic anhydride in the presence of pyridine.[3] In a similar manner the cyclohexyl derivative (4.6 g, 25 mmol), when treated with sodium hydride (25 mmol) followed by acetic anhydride (25 mmol), yielded 4.05 g (71%) of **8b**, bp 105–109 (0.5 mm).

Treatment of 4.90 g (25 mmol) of ω-methyl-ω-(methylsulfinyl)-acetophenone[1] with 0.6 g (25 mmol) of sodium hydride followed

(11) H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963).

(12) H. Böhme and H. Fischer, *Chem. Ber.*, **76**, 99 (1943).

(12a) NOTE ADDED IN PROOF.—We have now succeeded in preparing **12** by the addition of a solution of the enolate anion to methanesulfinyl chloride. As expected **12** is readily converted into the triketone.

(13) S. I. Miller, *J. Amer. Chem. Soc.*, **78**, 6091 (1956).

(14) W. M. Lauer and M. A. Spielman, *ibid.*, **53**, 1533 (1931).

(15) M. Balasubramian and V. Baliak, *J. Chem. Soc.*, 1844 (1954).

by 2.55 g (25 mmol) of acetic anhydride yielded 5.55 g of a yellow oil which hydrolyzed readily to yield the starting keto sulfoxide. The spectra of the oil indicated predominant O alkylation: ir ($CHCl_3$) 1770 (C=O), 1200 (C—O), 1047 cm^{-1} (SO).

ω-(Methylmercapto)-ω-(methylsulfonyl)acetophenone.—A solution of 9.1 g (50 mmol) of ω-(methylsulfinyl)acetophenone in 150 ml of THF was added with stirring to a suspension of 1.2 g of sodium hydride (50 mmol) in 25 ml of THF. After the evolution of hydrogen ceased, 5.0 g (51 mmol) of methanesulfinyl chloride[16] was added dropwise. The mixture was stirred for 1 hr and then poured into 300 ml of water. Extraction with chloroform followed by drying over magnesium sulfate and evaporation of the solvent gave 9.15 g (75%) of product: mp 100–111° (recrystallization from chloroform–ether gave mp 115–117°); ir ($CHCl_3$) 1675 (C=O), 1307 and 1110 cm^{-1} (SO_2); pmr ($CDCl_3$) δ 2.47 (s, 3), 3.23 (s, 3), 5.36 (s, 1), 7.4–7.7 (m, 3), 7.9–8.1 (m, 2).

Anal. Calcd for $C_{10}H_{12}O_3S_2$: C, 49.18; H, 4.95; S, 26.21. Found: C, 49.06; H, 4.91; S, 26.15.

Pummerer Rearrangement of ω-(Methylsulfinyl)acetophenone to Yield ω-Chloro-ω-(methylmercapto)acetophenone.—Treatment of 3.64 g (19 mmol) of the keto sulfoxide with 1.86 g (19 mmol) of methanesulfinyl chloride yielded 3.47 g (87%) of ω-chloro-ω-(methylmercapto)acetophenone: bp 108 (2 mm); pmr δ 2.18 (s, 3), 6.40 (s, 1). Identical material was formed by the reaction of the β-keto sulfoxide with thionyl chloride or by the reaction of phenylglyoxal hemimercaptal with thionyl chloride.[17]

(16) I. B. Douglas and D. R. Poole, *J. Org. Chem.*, **22**, 536 (1957); I. B. Douglas and B. S. Farsh, *ibid.*, **23**, 330 (1958).

(17) Unpublished results with L. A. Ochrymowycz.

3-(Methylmercapto)-3-(methylsulfonyl)-2,4-pentanedione (13a).—2,4-Pentanedione (10 g, 0.1 mol) in 100 ml of THF was added dropwise to a suspension of 2.4 g (0.1 mol) of sodium hydride in 25 ml of THF. After the evolution of hydrogen had ceased, 9.8 g (0.1 mol) of methanesulfinyl chloride was added cautiously. The mixture was stirred for 2 hr at 25° before dilution with 400 ml of water. Extraction with chloroform followed by drying over magnesium sulfate and evaporation of the solvent left 11.6 g of a yellow paste which could be recrystallized from chloroform–ether to give 7.0 g of **13a** (62%): mp 102.5–104°; ir 1721 (C=O), 1316 and 1130 cm^{-1} (SO_2); pmr ($CHCl_3$) δ 2.29 (s, 3), 2.41 (s, 6), 3.10 (s, 3).

Anal. Calcd for $C_7H_{12}O_4S_2$: C, 37.50; H, 5.40; S, 28.55. Found: C, 37.35; H, 5.41; S, 28.85.

Dibenzoyl(methylmercapto)(methylsulfonyl)methane (13b).—Substitution of 4.48 g (20 mmol) of dibenzoylmethane, 0.5 g (21 mmol) of sodium hydride, and 2.0 g (20 mmol) of methanesulfinyl chloride in the procedure used for the preparation of **13a** resulted in the formation (1.9 g, 56%) of **13b**: mp 143–144°; ir ($CHCl_3$) 1721 (C=O), 1316 and 1130 cm^{-1} (SO_2); pmr ($CDCl_3$) δ 2.20 (s, 3), 3.21 (s, 3), 7.2–7.6 (m, 6), 7.8–8.2 (m, 4).

Anal. Calcd for $C_{17}H_{16}O_4S_2$: C, 58.62; H, 4.63; S, 18.32. Found: C, 58.33; H, 4.71; S, 18.14.

Registry No.—**4**, 19916-60-0; **6**, 19916-61-1; C_6H_5CO-$CH(SCH_3)SO_2CH_3$, 19916-62-2; **13a**, 19916-63-3; **13b**, 19916-64-4.

β-Keto Sulfoxides. V. Condensation of Dimethyl Sulfoxide and Dimethyl Sulfone with Dibasic Esters[1]

Glen A. Russell, Edward T. Sabourin, and Gerhard Hamprecht

Department of Chemistry, Iowa State University, Ames, Iowa 50010

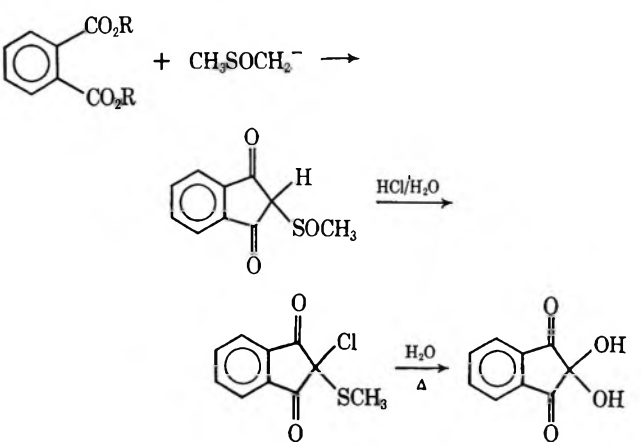
Received April 2, 1968

A new condensation reaction between two molecules of the methylsulfonyl carbanion ($CH_2SO_2CH_2^-$) or the methylsulfinyl carbanion ($CH_3SOCH_2^-$) and a variety of 1,2- 1,3- and 1,4-dicarboxylic esters is described. In favorable cases the condensation proceeds to yield an unsaturated monoketo disulfoxide or disulfone containing a new five-, six-, or seven-membered ring. Desulfurization of the disulfoxides and disulfones using Raney nickel has been investigated.

The condensation of esters of phthalic acid with the methylsulfinyl carbanion ($CH_3SOCH_2^-$) have been described.[2,3] 2-(Methylsulfinyl)-1,3-indandione is readily formed when the ester is added to a solution of sodium methoxide in dimethyl sulfoxide (DMSO). The methylsulfinylindandione was readily converted into ninhydrin *via* treatment with hydrochloric acid and hydrolysis of the resulting 2-chloro-2-(methylmercapto)-1,3-indandione (Scheme I). In dimethylformamide solution containing potassium *t*-butoxide a low yield of 2-(methylsulfonyl)-1,3-indandione was obtained from the reaction of ethyl phthalate with dimethyl sulfone ($DMSO_2$).[4]

Two other types of condensation can be imagined in the reaction of a dialkyl sulfoxide or dialkyl sulfone with the ester of a dibasic acid (paths b and c, Scheme II). We herein describe a study of a variety of reaction parameters of the nature of the condensation reaction between esters of dibasic acids and DMSO and $DMSO_2$. Our results are consistent with the expectation that the concentration of the carbanion is important in determining whether the product of process a or process b is formed.

Scheme I



A "low" concentration of the methylsulfinyl or methylsulfonyl carbanion was presumably involved in the previous work wherein the carbanions were generated by an acid–base equilibrium. In the present work we have also approached a low concentration of the carbanion by the dropwise addition of the irreversibly

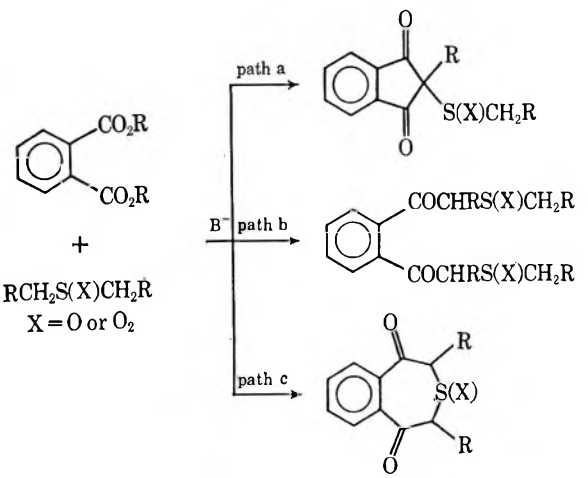
(1) This work was supported by the Army Office of Research (Durham). For part IV, see G. A. Russell and E. J. Sabourin, *J. Org. Chem.*, **34**, 2336 (1967).

(2) H.-D. Becker, G. J. Mikol, and G. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3410 (1963).

(3) H.-D. Becker, *J. Org. Chem.*, **29**, 1358 (1964).

(4) H.-D. Becker and G. A. Russell, *ibid.*, **28**, 1896 (1963).

SCHEME II



formed carbanion to the ester. We have utilized the reaction between sodium hydride and DMSO or $DMSO_2$ for the irreversible formation of the carbanion.[5] Condensations performed in the presence of "high" concentrations of the carbanions involved the addition of the ester to this carbanion solution.[6]

The dianion of DMSO[7] has also been examined in condensation with diethyl phthalate.

$$CH_3SOCH_3 + 2NaNH_2 \xrightarrow{NH_3} Na^+{}^-CH_2SOCH_2{}^-Na^+ + 2NH_3$$

Results and Discussion

The addition of diethyl phthalate to the irreversibly formed methylsulfinyl carbanion in DMSO solution, or to the dianion of DMSO in liquid ammonia,[7] failed to yield identifiable condensation products even though excellent yields of the indandione can be obtained by the use of the reversibly formed carbanion.[2] The difference in the two sets of experiments is apparently mainly connected with the concentration of the carbanion employed. Thus, the dropwise addition of the irreversibly formed methylsulfinyl carbanion to diethyl phthalate in DMSO solution results in the isolation of 31% 2-chloro-2-methylmercapto-1,3-indandione after acidification with hydrochloric acid. Addition of dimethyl phthalate to the product of the reaction of 2 equiv of sodium amide with each mole of DMSO in hexamethylphosphoramide solution led to the isolation of a low yield (14%) of a new type of condensation product identified as the 2:1 adduct **1a** (Scheme III).

The addition of diethyl phthalate to the preformed carbanion from $DMSO_2$ in THF solution gave rise to a mixture of the 2:1 condensation products, **1b** (10%) and **2** (70%). The formation of a low yield of 1:1 adduct, the indandione, by use of the irreversibly formed methylsulfinyl carbanion in THF solution (potassium *t*-butoxide as base) had been previously observed.[4] Treatment of **1b** with potassium *t*-butoxide in DMSO resulted in complete isomerization to **2**.

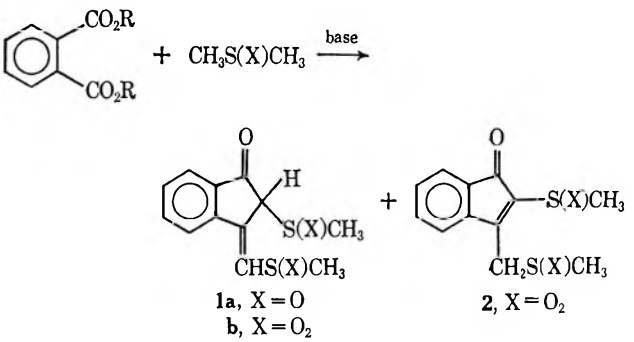
Dimethyl 2,3-naphthalenedicarboxylate underwent a similar series of reactions. Dropwise addition of the irreversibly formed carbanion to the diester resulted in

(5) E. J. Corey and M. J. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964); **87**, 1345 (1965).

(6) It should be recognized that solvation by the alcohol can also have an appreciable effect on the reactivity of the carbanium.

(7) E. M. Kaiser and R. D. Beard, *Tetrahedron Lett.*, 2583 (1968).

SCHEME III

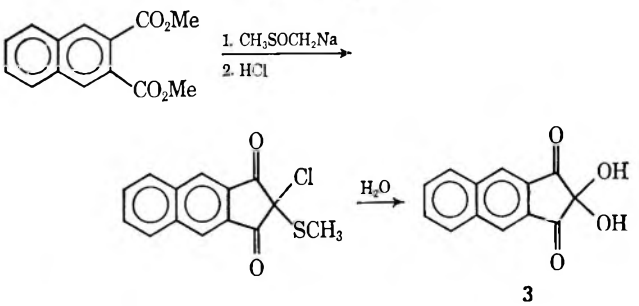


1a, X = O
b, X = O_2

2, X = O_2

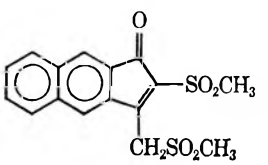
a 59% yield of 2-chloro-2-methylmercapto-1,3-naphthindandione which could be converted into the triketone hydrate **3** in an over-all yield of 45% based on the starting ester (Scheme IV). Addition of the ester to

SCHEME IV



3

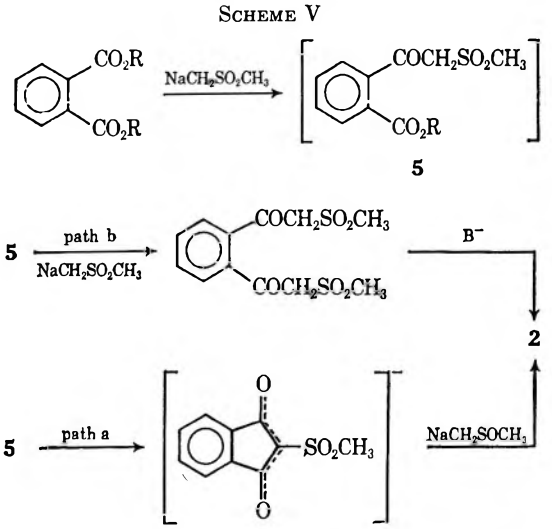
the preformed methylsulfonyl carbanion in THF solution gave an 84% yield of the 2:1 adduct, **4**.



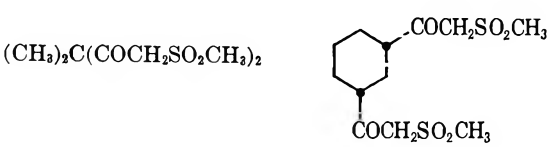
4

The products of this new condensation reaction appear to result from reaction path b followed by cyclization. However, the alternate formulation *via* addition of the methylsulfonyl carbanion to the product of reaction path a cannot be excluded (Scheme V).

SCHEME V

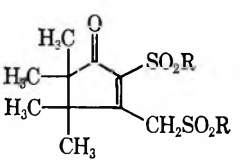


The formation of 2 from reaction path a suffers from the fact that the 2-methylsulfonyl-1,3-indandione is a very strong acid with a $pK_a < 0$.[4] It would thus exist solely in the anionic form in basic solutions and the addition would have to involve the reaction of two negative species. The formation of a low yield of the 2-methylsulfonyl-1,3-indandione when the ester is added to the carbanion generated by equilibrium with potassium *t*-butoxide but the formation of disulfones **1b** and **2** when the ester is added to a higher concentration of the preformed carbanions suggests that intermediate **5** can either cyclize to yield a monosulfone or react with another molecule of the methylsulfonyl carbanion to yield the disulfone which can then cyclize. Under the reaction condition diethyl dimethyl malonate condenses with two molecules of the methylsulfonyl carbanion to yield the disulfone **6**. Thus, when cyclization *via* path a is inhibited by steric considerations, further condensations *via* path b occurs readily. Similarly dimethyl *cis*-1,3-cyclohexanedicarboxylate yielded the disulfone **7**.



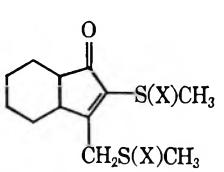
6 **7**

A variety of 1,2-dicarboxylic esters were examined under the conditions that produced **2**–**4**. Dimethyl succinate underwent self-condensation to yield only 2,5-dicarbomethoxy-1,4-cyclohexanedione when added to the preformed methylsulfonyl carbanion. However, dimethyl tetramethylsuccinate gave a cyclization reaction to yield 34% **8**.



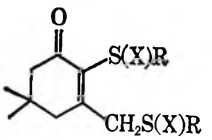
8

Diethyl *cis*-1,2-cyclohexanedicarboxylate reacted with the preformed methylsulfinyl carbanion in THF to yield the disulfoxide **9a** (29%). The analogous reaction with the methylsulfonyl carbanion produced a 93% yield of hexahydro-2-(methylsulfonylmethyl)-Δ^2-inden-1-one (**9b**).



9a, X = O
b, X = O_2

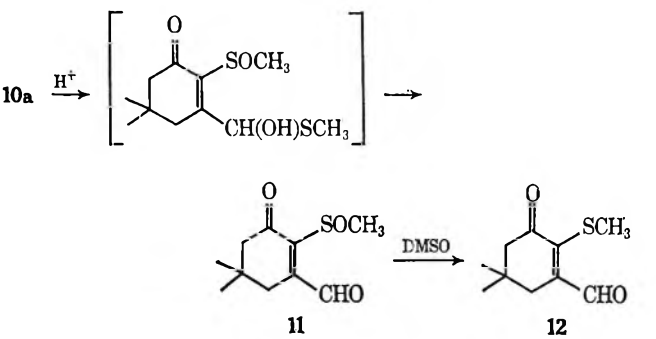
1,3-Dicarboxylic acid diesters underwent condensation with two molecules of DMSO or $DMSO_2$ (addition of the ester to the preformed carbanions). Dimethyl 3,3-dimethylglutarate yielded **10a** and **10b** in yields of 58 and 80%. Phenyl methyl sulfone yielded **10c** in 46% yield. The disulfone **10b** was also obtained (70% yield) when the ester was added to a mixture of



10a, X = O; R = CH_3
b, X = O_2; R = CH_3
c, X = O_2; R = C_6H_5

$DMSO_2$ and potassium *t*-butoxide in THF. Here cyclization *via* path a is apparently quite slow and even a low concentration of methylsulfonyl carbanion will divert the initial condensate to the disulfone. The isolation of **10a** was complicated by a facile rearrangement in the presence of acid. Two aldehydes were produced in DMSO solution with pmr absorption at δ 10.56 and 11.00. Apparently the Pummerer rearrangement[2] is occurring to yield **11** which reacts with DMSO to yield **12** (Scheme VI) which could be isolated in pure form and which had the δ 11.00 pmr absorption.

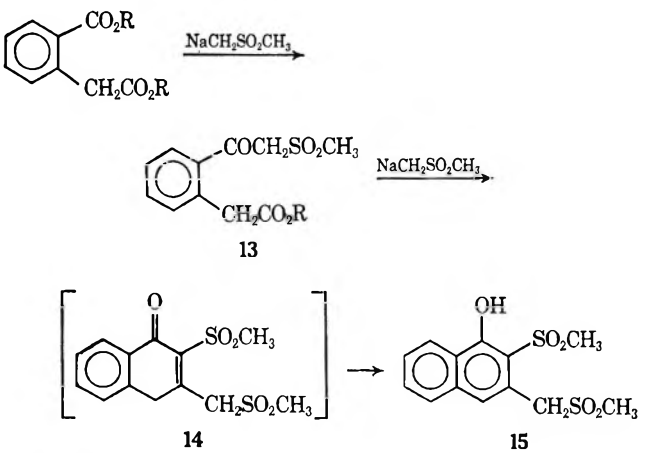
SCHEME VI



11 **12**

Dimethyl homophthalate when added to the preformed methylsulfonyl carbanion yielded **13** (isolated with R = H) and **15** (Scheme VII). Compound **13** is

SCHEME VII

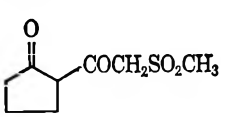


13

14 **15**

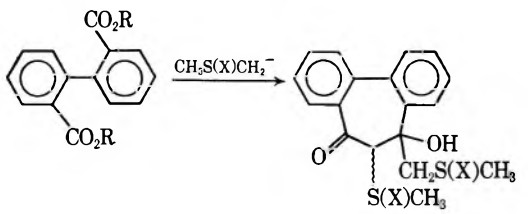
apparently a precursor to **14** and **15** since it was found only in reactions that had proceeded for periods of less than 2 hr. In a 20-hr experiment the yield of **15** was 95%.

Condensation of the methylsulfonyl carbanion with dimethyl adipate yielded only the monosulfone **16**.



16

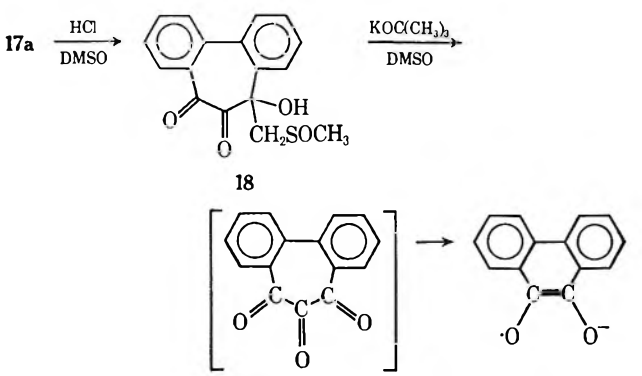
Diethyl diphenate reacted with the methylsulfinyl carbanion to produce **17a**. The disulfoxide was formed from both the carbanion preformed by sodium hydride or the equilibrium concentration generated by potassium *t*-butoxide. Probably the preferred *trans* conformation of the carboxyl groups retards the cyclization of process a and allows disulfoxide formation to occur. The disulfone **17b** could be prepared from the methylsulfonyl carbanion or by oxidation of **17a** was hydrogen peroxide. The resistance of **17a** to dehydration is



17a, X = O
b, X = O_2

noteworthy. Treatment with hydrochloric acid led to the Pummerer rearrangement product **18** which in basic solution yielded the esr spectrum of 9,10-phenanthrene semiquinone[8] (Scheme VIII). Other examples of

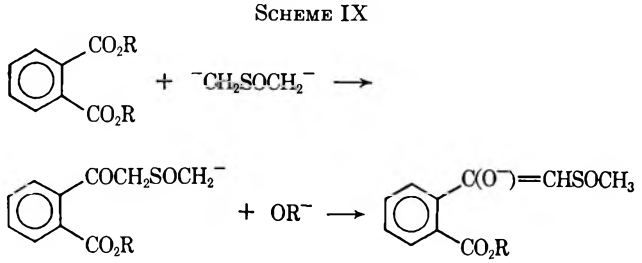
SCHEME VIII



triketone decarbonylations under similar conditions are known.[9]

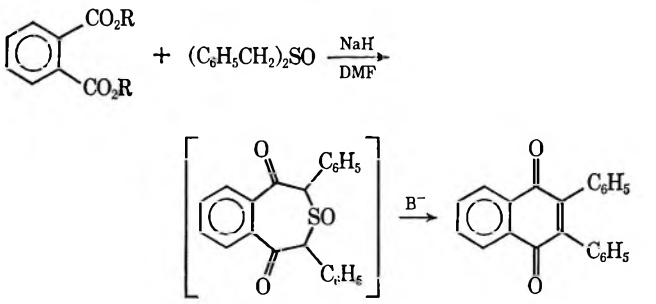
No evidence for the occurrence of process c from reaction of DMSO or $DMSO_2$ with diethyl phthalate had been found,[10] (Scheme IX). Even if the dianion

SCHEME IX



of the sulfone or sulfoxide is employed the acid–base equilibrium is unfavorable. We believe that process c occurred in the reaction of diethyl phthalate with a slurry of sodium hydride and dibenzyl sulfoxide in dimethyl-formamide at 60° (Scheme X). *trans*-Stil-

SCHEME X

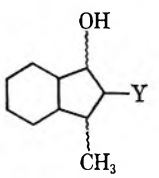


19

bene and a 24% yield of 2,3-diphenyl-1,4-naphthaquinone were isolated. Intermediate **19** is likely to be involved since it is known that dibenzyl sulfoxide is converted into stilbene under the reaction conditions.[11]

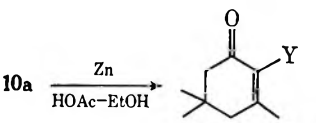
We have attempted to remove the sulfur from the cyclic disulfoxides and disulfones prepared in this work. The sulfoxide linkage is readily cleaved by reduction (*e.g.*, zinc and acid) when it is attached to a saturated carbon α to a carbonyl group.[12] We found that vinylogs ($RCOCH{=}CHCH_2SOCH_3$) are also readily cleaved.

Reduction of **9a** with W-2 Raney nickel[13] in refluxing alcohol gave 70% hexahydro-3-methyl-1-indanone in 5 hr. Larger reaction periods yielded a mixture of the isomeric alcohols (**20a**). The disulfone **9b** was reduced to a mixture of isomers **20b** by Raney nickel in refluxing ethanol.



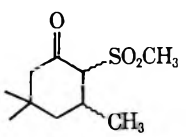
20a, Y = H
b, Y = SO_2CH_3

Reduction of **10a** by zinc in acetic acid–ethanol gave a 30% yield of **21a** accompanied by the sulfide **21b**.



21a, Y = $SOCH_3$
b, Y = SCH_3

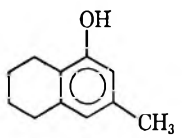
Reduction by aluminum amalgam in aqueous THF[5] gave a mixture of **21a** and **21b**. Refluxing a solution of **10a** in ethanol with Raney nickel gave a 64% yield of the isomeric 3,3,5-trimethylcyclohexanols. The sulfone **10c** could be reduced under similar conditions to yield the trimethylcyclohexanols in 47%. However, the sulfone **10b** was much more resistant to reduction. A reduction of **10b** to **22** in 94% yield was achieved by



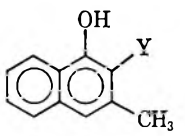
22

(8) M. Adams, M. S. Blois, Jr., and R. H. Sands, *J. Chem. Phys.*, **28**, 775 (1958); G. Vincow and G. K. Fraenkel, *ibid.*, **34**, 1333 (1961).
(9) G. A. Russell and S. A. Weiner, *J. Amer. Chem. Soc.*, **89**, 6623 (1967).
(10) W. E. Truce and F. J. Lotspeick, *ibid.*, **78**, 848 (1956).
(11) T. J. Wallace, H. Pabiner, J. E. Hofmann, and A. Schriesheim, *J. Chem. Soc.*, 1271 (1965).
(12) G. A. Russell and G. J. Mikol, *J. Amer. Chem. Soc.*, **88**, 5498 (1966).
(13) R. Mozingo, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 181.

addition of nickel–aluminum alloy to a solution of the sulfone in 10% aqueous sodium hydroxide at 90°.[14] The disulfone **15** was reduced by Raney nickel in refluxing ethanol to 3-methyl-5,6,7,8-tetrahydro-1-naphthol (**23**) in 36% yield. Reduction under the Papa–Schwenk–Whitman conditions yielded a mixture of **24a** and **24b**.



23



24a, Y = H
b, Y = SO_2CH_3

A number of condensations were attempted with dimethyl 1,8-naphthalenedicarboxylate, diethyl maleate, diethyl 2,3-dimethyl-maleate, diethyl oxalate, and diethyl carbonate. No isoluble condensation products were found with either the methylsulfonyl or the methylsulfinyl carbanions.

Experimental Section

Methylsulfinyl Carbanion.—Solutions of the methylsulfinyl carbanion were prepared and allowed to react in a dry, prepurified nitrogen atmosphere. Irreversible formation from sodium hydride and dimethyl sulfoxide was accomplished by the method of Corey and Chaykovsky.[5] Equilibrium solutions were formed from alkali metal alkoxides and DMSO.[2]

Methylsulfonyl Carbanion.—Solutions of the methylsulfonyl carbanion were prepared and allowed to react in a dry, prepurified nitrogen atmosphere in DMSO solution. Preparation was similar to that of the methylsulfinyl carbanion, but dimethyl sulfone was added to the mixture.

2-Chloro-2-(methylmercapto)-1,3-naphthindandione.—To 6.1 g of dimethyl 2,3-naphthalenedicarboxylate (25 mmol) in 50 ml of DMSO was added 50 ml of a DMSO solution of the methylsulfinyl carbanion prepared from 2.4 g of sodium hydride (0.1 mol). The addition was accomplished by a hypodermic over a 1-hr period. Vigorous stirring of the solution was essential. As soon as the addition was completed, the mixture was poured into 100 ml of ice water. The aqueous solution was extracted with ether and then added to 100 ml of 6 *N* hydrochloric acid at 0°. A precipitate of 2-chloro-2-methylmercapto-1,3-naphthindandione of 4.1 g (59%) was recovered by filtration: mp 154–155°; ir (CCl_4) 1718 (C=O), 1751 cm^{-1} (C=O); pmr ($CDCl_3$) δ 2.48 (s, 3), 7.6–7.9 (m, 2), 8.0–8.3 (m, 2), 8.53 (s, 2); mass spectrum (70 eV), *m/e* (rel intensity) 276 (100), 278 (39).

Anal. Calcd for $C_{14}H_9ClO_2S$: C, 60.76; H, 3.28; Cl, 12.81; S, 11.59. Found: C, 60.91; H, 3.46; Cl, 12.70; S, 11.45.

1,2,3-Naphthindantrione Hydrate (3).—To 1.5 g of the dimethyl 2,3-naphthalenedicarboxylate in 50 ml of DMSO at 10° was added dropwise (45 min) 100 ml of a 2 *M* solution of sodium hydride in DMSO. The reaction mixture was stirred for 2 hr before it was poured into 200 ml of concentrated hydrochloric acid at 0° with efficient stirring. After stirring for 9 hr, the hydrochloric acid solution was diluted with 1000 ml of water and extracted twice with 500 ml of ethyl acetate. The solvent was removed under vacuum to leave a dark oil that was boiled in water for 2 hr. The cooled, filtered aqueous solution was extracted with ethyl acetate, the solution was dried with sodium sulfate and the solvent was removed by vacuum. The residue was developed on a silica gel column with a 1:1 mixture of ethyl acetate–petroleum ether (bp 60–90°) distillate to yield 640 mg (45%) of the trione, recrystallized from a mixture of ethyl acetate and ether. The material lost water and turned green at 147° and melted at 282° (lit.[15] mp 279–282°). Both **3** and 2-chloro-2-(methylmercapto)-1,3-naphthindandione give a green color with amino acids.

2-(Methylsulfinyl)-3-(methylsulfinylmethylene)indanone (1a).—DMSO (100 mmol) was added to 205 mmol of sodium amide in 250 ml of liquid ammonia. After 3 hr the ammonia was allowed to evaporate and a mixture of 80 ml of hexamethylphosphoramide (HMPA) and 20 ml of ether was added. A mixture of 19.4 g (100 mmol) of dimethyl phthalate in 20 ml of ether was added slowly to the sodium amide solution at 10°. After stirring for 4 hr at 25° the reaction mixture was poured into 250 ml of ice water and extracted with five 40-ml portions of chloroform to remove the HMPA. The aqueous phase was acidified carefully to a pH of 1 by concentrated hydrochloric acid. Phthalamide was removed by filtration and the filtrate was extracted with six 30-ml portions of chloroform. Drying over magnesium sulfate and removal of the solvent under vacuum left 9.65 g of an oil which could be crystallized from acetonitrile–ether to give 3.75 g of **1a**: mp 141–143°; ir (KBr) 1720 (C=O), 1655, 1630 (C=C), 1042, 1025 cm^{-1} (SO); pmr ($CDCl_3$) δ 7.93–7.29 (m, 4), 7.18 (d, 1), 5.00 (d, 1, exchanged with D_2O), 2.92 (s, 3), 2.54 (s, 3).

Anal. Calcd for $C_{12}H_{12}O_3S_2$: C, 53.70; H, 4.50; S, 23.89. Found: C, 53.52; H, 4.54; S, 23.63.

2-(Methylsulfonyl)-3-(methylsulfonylmethyl)indenone (2).—Diethyl phthalate (5.55 g, 25 mmol) in 50 ml of THF was added to the methylsulfonyl carbanion prepared from 9.4 g of $DMSO_2$ (0.1 mol) and 2.4 g of sodium hydride (0.1 mol) in 50 ml of DMSO. After stirring for 3 hr at 25° the reaction mixture was poured cautiously into 100 ml of ice water, neutralized with dilute hydrochloric acid, and thoroughly extracted with chloroform. Removal of the chloroform under vacuum left 5.2 g of **2** (70%), a yellow solid: mp 175–178° (several recrystallizations from chloroform–methanol raised the melting point to 193–195°); ir (KBr) 1718 (C=O), 1608 (C=C), 1304, 1143 cm^{-1} (SO_2); pmr ($CDCl_3$) δ 3.17 (s, 3), 3.26 (s, 3), 4.98 (s, 2), 7.56 (s, 4); mass spectrum (70 eV), parent peak at *m/e* 300.

Anal. Calcd for $C_{12}H_{12}O_5S_2$ (300.2): C, 48.01; H, 4.03; S, 21.32. Found: C, 47.98, H, 4.05; S, 21.38.

An isomer of **2** identified as **1b** was isolated from the aqueous solution upon standing for 24 hr. Treatment of this material with a DMSO solution of potassium *t*-butoxide for 18 hr yielded a product with an ir spectrum superimposable with that of **2**. The yield of **1b** was 0.77 g (10%): mp 215–217°; ir (KBr) 1736 (C=O), 1608 (C=C), 1304, 1131 cm^{-1} (SO_2); pmr (CF_3CO_2H) δ 3.48 (s, 6), 6.18 (d, 1, J = 1.5 Hz), 7.40 (d, 1, J = 1.5 Hz), 7.7–8.2 (m, 4); mass spectrum (70 eV) identical with that of **2**.

2-(Methylsulfonyl)-3-(methylsulfonylmethyl)naphthindenone (4).—Dimethyl 2,3-naphthalenedicarboxylate (2.44 g, 10 mmol) in 10 ml of DMSO was added dropwise at 25° to a solution of methylsulfonyl carbanion prepared from 3.8 g of dimethyl sulfone (40 mmol) and 1 g of sodium hydride (40 mmol) in 25 ml of DMSO. After stirring for 3 hr, the mixture was cautiously poured into 200 ml of water and acidified with hydrochloric acid. Filtration of the yellow precipitate formed upon acidification gave 2.94 g (84%) of **4**, mp 225–235° dec. Recrystallization from acetic acid–ethanol gave material with mp 244–246° dec; ir (KBr) 1700 (C=O), 1623 (C=C), 1307, 1136 cm^{-1} (SO_2); pmr (CF_3CO_2H) δ 3.47 (s, 3), 3.52 (s, 3), 5.37 (s, 2), 7.6–8.2 (m, 6).

Anal. Calcd for $C_{16}H_{14}O_5S_2$: C, 54.86; H, 4.03; S, 18.27. Found: C, 54.85; H, 4.06; S, 18.27.

3,3-Dimethyl-1,5-di(methylsulfonyl)-2,4-pentanedione (6).—Diethyl dimethylmalonate (4.7 g, 25 mmol) in 50 ml THF was added to the methylsulfonyl carbanion prepared from 9.4 g of dimethyl sulfone (0.1 mol) and 2.4 g sodium hydride (0.1 mol) in 50 ml of DMSO. The product was isolated as described in the preparation of **2** to yield 1.15 g (16%) of **6**: mp 107–108°; ir (KBr) 1706 (C=O), 1307, 1126 cm^{-1} (SO_2); pmr (CF_3CO_2H) δ 1.57 (s, 6), 3.01 (s, 6), 4.62 (s, 4).

Anal. Calcd for $C_9H_{16}O_6S_2$: C, 38.03; H, 5.67; S, 22.52. Found: C, 38.14; H, 5.66; S, 22.45.

ω,ω-Di(methylsulfonyl)-*cis*-1,3-diacetylcyclohexane (7).—Substitution of 5.0 g of dimethyl *cis*-1,3-cyclohexanedicarboxylate (20 mmol) in the procedure used for the preparation of **2** yielded 5.25 g (65%) of **7** as a white solid, mp 153–155°. Recrystallization from chloroform containing a trace of methanol gave material with mp 157–158°; ir (KBr) 1706 (C=O), 1307, 1127 cm^{-1} (SO_2); pmr (CF_3CO_2H) δ 3.30 (s, 6), 4.57 (s, 4).

Anal. Calcd for $C_{12}H_{20}O_6S_2$: C, 44.44; H, 6.22; S, 19.74. Found: C, 44.37; H, 5.93; S, 19.89.

2-(Methylsulfonyl)-3-(methylsulfonylmethyl)-4,4,5,5-tetramethylcyclopentenone (8).—Substitution of 2.20 g of diethyl tetramethylsuccinate (10 mmol) in the procedure used for the preparation of **2** yielded 1.9 g of a pasty solid. Recrystallization from ethyl acetate and from chloroform–ether mixtures gave 1.03 g (34%) of **8**: mp 179.5–180.0°; ir ($CHCl_3$) 1727 (C=O), 1610

(14) D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942); E. Schwenk, D. Papa, B. Whitman, and H. Ginsberg, *ibid.*, **9**, 1 (1944).

(15) R. Meier and H. G. Lotter, *Chem. Ber.*, **90**, 222 (1957).

(C=C), 1311, 1130 cm^{-1} (SO_2); pmr ($CDCl_3$) δ 1.10 (s, 6), 1.20 (s, 6), 3.17 (s, 3) 3.21 (s, 3), 4.82 (s, 2).

Anal. Calcd for $C_{12}H_{20}O_5S_2$: C, 46.75; H, 6.54; S, 20.76. Found: C, 46.70; H, 6.50; S, 20.70.

Hexahydro-2-(methylsulfinyl)-3-(methylsulfinylmethyl)-Δ^2-inden-1-one (9a).—A solution of 5.7 g of diethyl *cis*-1,2-cyclohexanedicarboxylate (25 mmol) in 50 ml of THF was added dropwise to a solution of the methylsulfinyl carbanion prepared from 2.4 g (0.1 mol) of sodium hydride and 50 ml of DMSO. The mixture was stirred for 3 hr at 25°, then poured cautiously into 100 ml of ice water, carefully neutralized with hydrochloric acid, and thoroughly extracted with chloroform. The extracts were dried by magnesium sulfate and the solvent was evaporated to give 2.3 g (29%) of **9a** as a white solid: mp 131–134° (recrystallization from chloroform–ether raised the melting point to 134–137° dec); ir ($CHCl_3$) 1700 (C=O), 1590 (C=C), 1047 cm^{-1} (SO); pmr ($CDCl_3$) broad absorption at δ 1.0–3.0 with methyl singlets at 2.72 and 2.99, total area 16 [the methylene hydrogens adjacent to the sulfoxide group gave an AB pattern at δ 3.98 and 4.90 (J = 12 Hz)].

Anal. Calcd for $C_{12}H_{18}O_3S_2$: C, 52.55; H, 6.62; S, 23.34. Found: C, 52.41; H, 6.65; S, 23.47.

Hexahydro-2-(methylsulfonyl)-3-(methylsulfonylmethyl)-Δ^2-inden-1-one (9b).—Substitution of 5.7 g of diethyl *cis*-1,2-cyclohexanedicarboxylate (25 mmol) in the procedure used for the preparation of **2** gave 6.6 g (93%) of **9b**: mp 141–144° (recrystallization from methanol raised the melting point to 143–144°); pmr ($CDCl_3$) δ 1.0–3.0 (m, 10), 3.12 (s, 3), 3.20 (s, 3), 4.18, 5.40 (AB quartet, 2, J = 12 Hz, $CH_2SO_2CH_3$).

Anal. Calcd for $C_{12}H_{18}O_5O_2$: C, 47.06; H, 5.63; S, 20.90. Found: C, 47.00; H, 5.71; S, 20.83.

5,5-Dimethyl-2-(methylsulfinyl)-3-(methylsulfinylmethyl)-Δ^2-cyclohexenone (10a).—Substitution of 4.7 g of dimethyl 3,3-dimethylglutarate (25 mmol) in the process described for the preparation of **9** resulted in the formation of a yellow oil that produced 3.0 g (46%) of **10a**, mp 68–81° upon trituration with cold ether. An additional 0.8 g of **10a** was isolated from the filtrate by column chromatography. In addition column chromatography yielded 0.3 g of 5,5-dimethyl-2-(methylmercapto)-3-carboxaldehyde-2-cyclohexenone (**12**). The wide melting point range of **10a** could not be improved by recrystallization from chloroform–ether and it is concluded that **10a** was a mixture of the racemic pairs of the two possible diastereomers: ir ($CHCl_3$) 1664 (C=C), 1597 (C=C), 1036 cm^{-1} (SO); pmr ($CDCl_3$) δ 1.11 (s, 6), 2.40 (s, 2), 2.65 (s, 2), 2.75 (s, 3), 2.97, 2.99 (singlets, total intensity 3), 3.6–5.2 (m, 2; analyzed as two AB quartets, 3.70 and 4.78, J = 11.6 Hz, and 4.18 and 5.01, J = 11.0 Hz).

Anal. Calcd for $C_{11}H_{18}O_3S_2$: C, 50.37; H, 6.92; S, 24.90. Found: C, 50.47; H, 7.00; S, 24.68.

Compound **12** was identified by its mass, ir, and pmr spectrum: the mass spectrum gave a parent peak at m/e 198 and, from the intensity of $(M + 2)^+$ = 6% of M^+, it could be concluded that only one sulfur atom was present; ir (CCl_4) 1686 (C=O), 1672 cm^{-1} (C=O); pmr (CCl_4) δ 1.65 (s, 6), 2.40, 2.73 (singlets, total intensity 7), 10.56 (s, 1).

5,5-Dimethyl-2-(methylsulfonyl)-3-(methylsulfonylmethyl)-Δ^2-cyclohexenone (10b).—Substitution of 4.7 g of dimethyl 3,3-dimethylglutarate (25 mmol) in the process described for the preparation of **2** resulted in the formation of 5.9 g (80%) of **10b**: mp 150–162° (recrystallization from chloroform raised the melting point to 174.0–174.5°); ir ($CHCl_3$) 1686 (C=O), 1600 (C=C), 1307, 1131 cm^{-1} (SO_2); pmr ($CDCl_3$) δ 1.09 (s, 6), 2.45 (s, 2), 2.79 (s, 2), 3.08 (s, 3), 3.27 (s, 3), 4.88 (s, 2).

Anal. Calcd for $C_{11}H_{18}O_5S_2$: C, 44.90; H, 6.17; S, 21.76. Found: C, 45.06; H, 6.13; S, 21.78.

Compound **10b** was formed but only in low yield when 25 mmol of sodium hydride and $DMSO_2$ were employed. Use of 0.1 mol of potassium *t*-butoxide and 0.1 mol of $DMSO_2$ gave a 70% yield of **10b**. Use of 0.1 mol of potassium *t*-butoxide and 25 mmol of $DMSO_2$ gave **10b** in 22% yield. Inverse addition of 0.1 mol of the methylsulfonyl carbanion gave **10b** in 31% yield.

5,5-Dimethyl-2-(phenylsulfonyl)-3-(phenylsulfonylmethyl)-Δ^2-cyclohexenone (10c).—Substitution of 4.7 g of dimethyl 3,3-dimethylglutarate (25 mmol) and 15.6 g of phenylmethyl sulfone (0.1 mmol), in the process described for the preparation of **2**, yielded 4.8 g (46%) of **10c**: mp 205–207°; ir ($CHCl_3$) 1686 (C=O), 1590 (C=C), 1311, 1144 cm^{-1} (SO_2); pmr ($CDCl_3$) δ 1.03 (s, 6), 2.27 (s, 2), 2.90 (s, 2), 5.12 (s, 2), 7.4–8.2 (m, 10).

Anal. Calcd for $C_{21}H_{22}O_5S_2$: C, 60.28; H, 5.30; S, 15.30. Found: C, 60.66; H, 5.35; S, 15.10.

2-(Methylsulfonyl)-3-(methylsulfonylmethyl)-1-naphthol (15).—Substitution of 10.4 g of dimethyl homophthalate (50 mmol) and extending the reaction period to 24 hr in the preparation described for **2** yielded 14.9 g (95%) of **15**, mp 194–200°, as a solid upon acidification [recrystallization (CH_3CO_2H) gave mp 200–202°]: ir (KBr) 3450 (OH), 1307, 1261 cm^{-1} (SO_2); pmr (DMSO) δ 3.02 (s, 3), 3.52 (s, 3), 5.25 (s, 2), 10.5–11.5 (s, 1, OH exchangeable with d_6-DMSO), 7.5–8.5 (m, 5); mass spectrum (70 eV), m/e (rel intensity) 3.4 (100), 316 (109.6).

Anal. Calcd for $C_{13}H_{14}O_5S_2$: C, 49.68; H, 4.49; S, 20.36. Found: C, 50.00; H, 4.47; S, 20.58.

If reaction periods of 3 hr are employed for the synthesis of **15**, the yield is lower and **13** (R = H) can be isolated. ***o*-(Methylsulfonylacetyl)phenylacetic acid** crystallizes slowly from the aqueous layer after **15** has been removed by filtration: the mass spectrum gave a molecular ion at 256 and from the $(M + 2)^+$ peak the presence of one sulfur atom was indicated; ir (KBr) 3570–2500 (OH), 1686, 1706 (C=O), 1302, 1236 cm^{-1} (SO_2); pmr of methyl ester ($CDCl_3$), δ 3.12 (s, 3), 3.68 (s, 3), 3.95 (s, 2), 4.57 (s, 2), 7.2–8.0 (m, 4).

2-(Methylsulfonylacetyl)cyclopentanone (16).—Substitution of 4.35 g of dimethyl adipate (25 mmol) in the preparation described for **2** yielded 3.45 g (67%) of **16**: mp 90–95° (recrystallization from chloroform raised the melting point to 98–100°); ir ($CHCl_3$) 3570–2500 (OH), 167°, 1706 (C=O), 1613 (C=C), 1316, 1429 cm^{-1} (SO_2); pmr ($CDCl_3$) δ 1.8–2.9 (m, 6), 3.91 (s, 2), 13 (broad singlet exchangeable with D_2O).

Anal. Calcd for $C_8H_{12}O_4S$: C, 47106; H, 5.92; S, 15.67. Found: C, 47.17; H, 5.98; S, 15.80.

The spectroscopic data indicated an appreciable enol content which was supported by a positive ferric chloride test.

3-Hydroxy-2-(methylsulfinyl)-3-(methylsulfinylmethyl)dibenzocycloheptanone (17a).—Substitution of 14.9 g of diethyl diphenate (50 mmol) in the preparation described for **9a** gave 14.3 g (79%) of **17a**, mp 150–177°. The same product was obtained using potassium *t*-butoxide as the base. The melting point of **17a** could not be improved by recrystallization. Thus, **17a** is probably a mixture of the racemic modifications of the possible diastereomers. Compound **17a** was insoluble in numerous solvents: its pmr spectrum was not determined; ir (KBr) 3448 (OH), 1672 (C=O), 1038 cm^{-1} (SO); mass spectrum (70 eV), m/e $(M)^+$ 362, $(M - 18)^+$ 344 (strong).

Anal. Calcd for $C_{18}H_{18}O_4S_2$: C, 59.66; H, 5.01; S, 17.66. Found: C, 59.51; H, 5.13; S, 17.74.

Additional proof of structure for **17a** was furnished by reduction to **3-hydroxy-3-(methylsulfinylmethyl)dibenzocycloheptanone** by zinc dust in acetic acid–ethanol.[12] From 8.7 g of **17a**, 20 g of zinc, and 150 ml of solvent, there was obtained after 3 hr at 25° 5.25 g (87%) of 3-hydroxy-3-(methylsulfinylmethyl)dibenzocycloheptanone: mp 160–168°; ir (KBr) 3175 (OH), 1667 (C=O), 1005 cm^{-1} (SO); pmr ($CDCl_3$) δ 2.32, 2.35 (singlets, total intensity 3), 3.07 (s, 2), 3.3–3.6 (m, 2), 5.41 (s, 1), 7.3–8.1 (m, 8).

Anal. Calcd for $C_{17}H_{16}O_3S$: C, 67.99; H, 5.37; S, 10.66. Found: C, 68.08; H, 5.11; S, 10.62.

Compound **17a** readily underwent the Pummerer rearrangement to yield **3-hydroxy-3-(methylsulfinylmethyl)dibenzo-1,2-cycloheptanedione (18).** In DMSO solution, to 1 g of **17a** in 10 ml of DMSO, was added 3 ml of water and 2 ml of concentrated hydrochloric acid at 25°. After 24 hr, the mixture was added to 25 ml of water and extracted with chloroform. The extract was dried with magnesium sulfate and the solvent was evaporated to yield a yellow paste. Treatment with ether containing a trace of methanol gave an unstable product **18**: mp 170–180°; ir (KBr) 3226 (OH), 1718, 1686 (C=O), 1020 cm^{-1} (SO); pmr (CF_3CO_2H, must be recorded rapidly), δ 2.62 (s, 3), 3.60, 4.02 (AB quartet, 2, J = 14 Hz), 7.5–8.2 (m, 8); esr (DMSO plus potassium *t*-butoxide) 1.68 (4 H), 0.4 (4 H) G; mass spectrum (70 eV), m/e 314.

3-Hydroxy-2-(methylsulfonyl)-3-(methylsulfonylmethyl)dibenzoheptanone (17b).—Substitution of 7.45 g of diethyl diphenate (25 mmol) in the process described for the preparation of **2** gave 9.15 g (92%) of **17b**: mp 173–177° [recrystallization (CH_3CO_2H) gave mp 187–188°]; ir (KBr) 3390 (OH), 1669 (C=O), 1299, 1129 cm^{-1} (SO_2); pmr ($CFCO_2H$) δ 3.22 (s, 6), 4.80 (broad singlet, 3), 7.2–8.0 (m, 8).

Anal. Calcd for $C_{18}H_{18}O_6S_2$: C, 54.82; H, 4.60; S, 16.23. Found: C, 54.70; H, 4.65; S, 16.23.

2,3-Diphenyl-1,4-naphthaquinone.—Dibenzyl sulfoxide (3.5 g, 15 mmol) and 1.5 g of sodium hydride (60 mmol) were stirred in

100 ml of DMF at 70°. Diethyl phthalate (3.4 g, 15 mmol) was added dropwise and the reaction mixture was stirred for 1 hr at 70° and 2 hr at 25°. The reaction mixture was added cautiously to water and the solution was extracted with ether. Removal of the ether left an oil that was chromatographed on an alumina column. A trace of *trans*-stilbene was eluted by hexane. A 1:1 hexane–benzene mixture eluted 1.1 g (24%) of the quinone, mp 132–138°. Recrystallization (CH_3CO_2H) gave mp 139.5–140.5° (lit.[16] mp 139–140°).

Reductions of 9a, 9b, 10a, 10b, 10c, and 15 by Raney Nickel.—Compound **9a** (567 mg) was stirred with 15 g of W-2 Raney nickel in 250 ml of refluxing ethanol for 5 hr. After cooling the mixture was filtered through a sintered-glass funnel and the residue was thoroughly washed with ethanol (caution, the residue is pyrophoric). Vacuum evaporation of the solvent left 221 mg (70%) of **hexahydro-3-methyl-1-indanone**: ir (CCl_4) 1739 cm^{-1} (C=O); pmr (CCl_4) δ 0.8–2.6 (m), 7.02 (d, J = 6.5 Hz). The material formed a 2,4-dinitrophenylhydrazone, mp 151–153° (lit.[17] mp 152–154°).

Treatment of **9b** (2.0 g) with 50 g of Raney nickel in 200 ml of refluxing ethanol in the manner described for 9a yielded 550 mg of a pasty solid that was eluted from Florisil with chloroform to give 373 mg (25%) of **hexahydro-2-(methylsulfonyl)-3-methyl-1-indanol (20b)**: mp 151°; ir ($CHCl_3$) 3536 (OH), 1290, 1122 cm^{-1} (SO_2); pmr ($CDCl_3$ δ 0.8–2.4 (m, 14 total), 1.18 (d, J = 6.5 Hz), 2.6–2.8 (broad s, 1, exchangeable with D_2O), 2.9–3.2 (m, 4), 3.05 (s), 3.7–4.1 (m, 1).

Anal. Calcd for $C_{11}H_{20}O_3S$: 56.88; H, 8.68; S, 13.78. Found: C, 56.92; H, 8.40; S, 13.49.

Reduction of **10a** (2.0 g) in 200 ml of ethanol by 50 g of Raney nickel according to the procedure given for **9a** yielded 642 mg (64%) of **3,3,5-trimethylcyclohexanol** which solidified upon the addition of a seed crystal of an authentic sample prepared by a two-step reduction (hydrogen over Pd on C followed by $NaBH_4$) of isophorone. The ir spectra of the two samples were superimposable. 3,3,5-Trimethylcyclohexanol was also prepared from **10c** (500 mg) by treatment with 40 g of Raney nickel in 200 ml of refluxing ethanol for 12 hr. The yield of alcohol was 69 mg (47%).

Treatment of **10b** with Raney nickel in ethanol for periods up to 48 hr yielded only mixtures of sulfones. Where 10 g of the nickel–aluminum alloy was added in small portions to 3 g of **10b** in 100 ml of 10% aqueous sodium hydroxide with vigorous stirring, there was obtained after 1 hr 2.09 g (94%) of **2-(methylsulfonyl)-3,5,5-trimethylcyclohexanone (22)**. The ketone was isolated by filtration of the hot solution, followed by neutralization with hydrochloric acid, and extraction with chloroform. After the extracts were dried over magnesium sulfate, the solvent was evaporated to give material with mp 67–70° [recrystallization (ether) gave mp 71–72°]; ir (CCl_4) 1706 (C=O), 1309, 1134 cm^{-1} (SO_2); pmr (CCl_4) δ 1.02 (s, 6) 1.30 (d, 3, J = 6.5 Hz), 1.5–1.7 (m, 2 H), 2.3 (broad s, 2), 2.4–2.9 (m, 1), 2.97 (s, 3), 3.50 (d, 1, J = 10 Hz).

Anal. Calcd for $C_{10}H_{18}O_3S$: C, 55.03; H, 8.31; S, 14.66. Found: C, 55.08; H, 8.30; S, 14.69.

Compound **15** (2.0 g) when treated in the manner described for **9a** yielded 372 mg (36%) of **3-methyl-5,6,7,8-tetrahydro-1-naphthol (23)**: mp 95–96° (from hexane) (lit.[18] mp 98.5°); pmr (CCl_4) δ 1.5–2.0 (m, 4), 2.11 (s, 3), 2.3–2.8 (m, 4), 5.12 (s, 1, exchangeable in D_2O), 6.10 (broad s, 1), 6.33 (broad s, 1); mass spectrum (70 eV), m/e 162.

Treatment of 2.0 g of **15** in the manner previously described for **10b** by 15 g of aluminum–nickel alloy gave 1.55 g of an oil analyzed by pmr to contain 28% **3-methyl-1-naphthol (24a)** and 50% **2-(sulfonylmethyl)-3-methyl-1-naphthol (24b)**. Treatment of the oil with hexane dissolved **24a** and left **24b** as a semisolid mass. Cooling the hexane solution produced crystals of **24a**: mp 88–89° (lit.[18] mp 89.0–89.5°); pmr (CCl_4) δ 2.30 (s, 3), 5.52 (s, 1, exchangeable with D_2O), 6.45 (d, 1, J = 1.5 Hz), 7.1–7.8 (m, 4), 7.9–8 (m, 1). Recrystallization of the hexane-insoluble material from ether yielded **24b**: mp 93.5–94°; ir (CCl_4) 3195 (OH), 1399, 1258 cm^{-1} (SO_2); pmr ($CDCl_3$) δ 2.65 (s, 3), 3.15 (s, 3), 7.0–7.6 (m, 4), 8.2–8.4 (m, 1), 11.05 (s, 1, exchangeable with D_2O).

Anal. Calcd for $C_{12}H_{12}O_3S$: C, 61.01; H, 5.12; S, 13.55. Found: C, 60.96; H, 5.07; S, 13.50.

2-(Methylsulfinyl)-3,5,5-trimethyl-Δ²-cyclohexenone (21a).—Compound **10a** (9.2 g) was reduced with 20 g of zinc dust in 600 ml of acetic acid–ethanol (60:40) for 1 hr.[12] The mixture was filtered, neutralized with sodium bicarbonate, and extracted with benzene. Evaporation of the benzene left 2.2 g (13%) of **21a**: mp 77–78°; ir ($CHCl_3$) 1667 (C=O), 1605 (C=C), 1042 cm^{-1} (SO); pmr ($CDCl_3$) δ 1.05 (s, 6), 2.32, 2.38 (s, total 7), 2.90 (s, 3).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.98; H, 8.05; S, 15.98. Found: C, 59.88; H, 8.19; S, 15.89.

If the reduction was continued for a longer period of time a number of side products were formed including **2-(methylmercapto)-3,5,5-trimethyl-Δ³-cyclohexenone (21b)**: bp 82–84° (0.5 mm); pmr ($CDCl_3$) δ 1.02 (s, 6), 2.21 (broad s, 6), 2.35 (broad s, 4). Compound **21b** could be oxidized to **21a** by sodium metaperiodate.

Registry No.—Dimethyl sulfoxide, 67-68-5; dimethyl sulfone, 67-71-0; 2-chloro-2-(methylmercapto)-1,3-naphthindandione, 19916-37-1; 3-hydroxy-3-(methylsulfinylmethyl)dibenzocycloheptanone, 19916-51-9; **1a**, 19916-38-2; **2**, 19916-39-3; **4**, 19955-00-1; **6**, 19916-40-6; **7**, 19933-73-4; **8**, 21647-19-8; **9a**, 19916-41-7; **9b**, 19916-43-9; **10a**, 19916-44-0; **10b**, 19916-45-1; **10c**, 19916-46-2; **13** (R = H), 19916-47-3; **15**, 19916-48-4; **16**, 19916-49-5; **17a**, 19916-50-8; **17b**, 19916-52-0; **18**, 19916-53-1; **20b**, 19916-54-2; **21a**, 19916-55-3; **21b**, 19916-56-4; **22**, 19955-01-2; **24b**, 19916-57-5.

(16) M. M. Shemyakin, D. A. Bochvar, and L. A. Shchukino, *Zh. Obshch. Khim.*, **22**, 439 (1952); *Chem. Abstr.*, **47**, 2741*f* (1953).

(17) L. N. Ivanova, T. A. Severina, G. A. Kogan, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1438 (1963); *Chem. Abstr.*, **59**, 13838*b* (1963).

(18) D. K. Datta and P. Bagchi, *Sci. Cult.* (*Calcutta*) **17**, 525 (1952).

Stereoselectivity in the Nonconcerted Reductive Rearrangement of Some Bicyclic Spiro Oxides[1]

ROBERT S. BLY AND GEORGE B. KONIZER

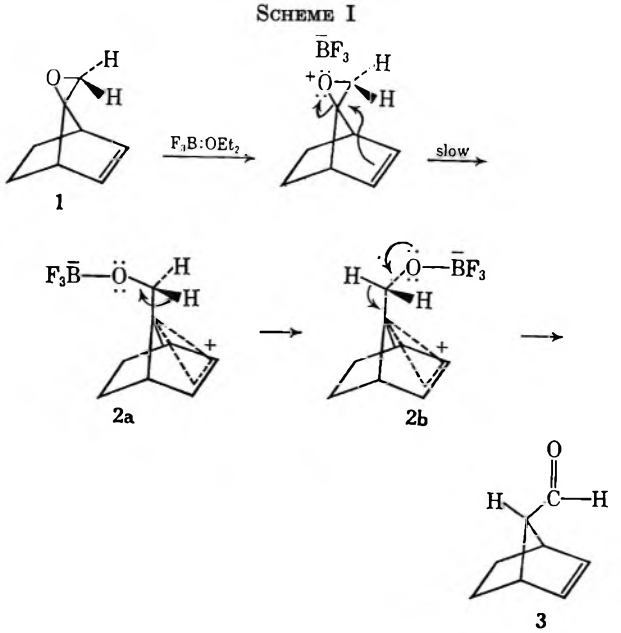
Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received November 21, 1968

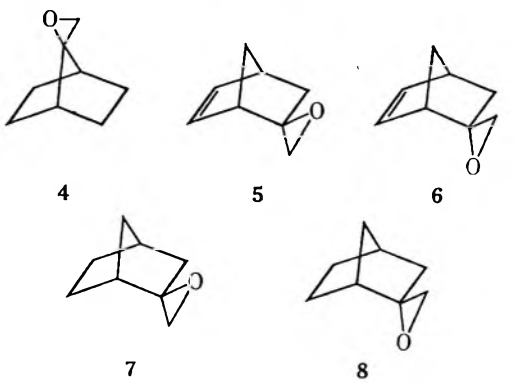
The reductive rearrangement of the series of bicyclic spiro oxides 1 and 4–8 has been examined using mixtures of lithium aluminum deuteride (or hydride) and aluminum trichloride. Three types of monodeuterated products are found: primary-deuterated tertiary alcohol in the case of 4 and 6, tertiary-deuterated primary alcohol in the case of 1, and α-deuterated primary alcohol in the case of 5–8. The stereochemistry of the products has been determined in each case and the mechanisms of the reductions are discussed. Evidence is presented in the cases of 1, 6, and 8 that the reductive rearrangement occurs exclusively or predominately in a nonconcerted fashion by way of a zwitterionic intermediate. It is suggested that the tendency of a terminal spiro oxide to be reduced in a nonconcerted fashion, in addition to being dependent upon the nature of the reducing species in solution, is governed by the stability of the cationic portion of the intermediate. Further, it is suggested that the tendency of such an intermediate to react by hydride migration (internal nucleophilic attack) rather than deuteride (or hydride) transfer from the coordinated alane (external nucleophilic attack) is governed by the extent of charge delocalization in the cationic portion of the intermediate. Finally, the ratio of *exo/endo* attack by the internal nucleophile, hydride, in the intermediates formed during the reduction of 6 and 8 is shown to be unusually low for a carbonium ion type of process, 3.3–7.1 and ~5.2, respectively. It is suggested that these ratios are consistent with the idea of steric hindrance to *endo* attack on the norbornyl ion or with the operation of a torsional effect.

During the course of an investigation directed toward the synthesis of 7-functionally substituted norbornenes we observed that spiro[2-norbornen-*anti*-7,2′-oxacyclopropane] (1) is converted stereoselectively into 2-norbornen-*syn*-7-carboxaldehyde (3) by heat and/or Lewis acids.[2] Because epoxides normally rearrange in a concerted fashion with inversion of configuration at the migration terminus[3] we suggested that the reaction in this case is nonconcerted and probably involves the charge-delocalized intermediate 2[2] (Scheme I).

SCHEME I



With the expectation that their rearrangements may also occur *via* cationic intermediates similar to those which had previously been investigated under solvolytic conditions,[4] we attempted to extend our studies to include the spiro oxides 4–8.[5] We found that the results



were stereochemically meaningless in these cases because the aldehydic products were epimerized and/or polymerized under the reaction conditions.[6] Since the extensive investigations of Eliel and coworkers had demonstrated that terminal oxides could be converted into mixtures of primary and secondary or tertiary alcohols by treatment with lithium aluminum hydride and aluminum trichloride,[7] it appeared that the epoxides 1 and 4–8 should react with lithium aluminum deuteride–aluminum trichloride mixtures to yield stable products of three types: primary alcohols having a tertiary deuterium, primary alcohols with a primary (α) deuterium label, and tertiary alcohols containing a primary deuterium (*viz.*, Scheme II). Thus an examination of the product distribution and stereochemistry in each case might allow us (1) to distinguish those products that were formed in a nonconcerted manner,

(1) Portions of this work have been presented before the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstract K8; the 39th Meeting of the South Carolina Academy of Science, Clinton, S. C., April 1966 [*Bull. S. Carolina Acad. Sci.*, **28**, 46 (1966)]; and the 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967, Abstract 26.

(2) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

(3) *Cf.* ref 2, footnotes 26–29.

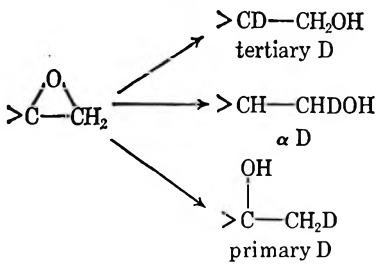
(4) For recent reviews, see (a) J. A. Berson in "Molecular Rearrangements," P. De Mayo, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 111 ff; (b) B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms—1965," Interscience Publishers, New York, N. Y., 1966, p 1 ff; (c) B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms—1966," Interscience Publishers, New York, N. Y., 1967, p 1 ff.

(5) (a) R. S. Bly, C. M. DuBose, Jr., and G. B. Konizer, *J. Org. Chem.*, **33**, 2188 (1968); (b) R. K. Bly and R. S. Bly, *ibid.*, **34**, 304 (1969).

(6) G. B. Konizer, Ph.D. Dissertation, Department of Chemistry, University of South Carolina, 1968.

(7) (a) E. L. Eliel and D. W. Delmonte, *J. Amer. Chem. Soc.*, **80**, 1744 (1958); (b) E. L. Eliel and M. N. Rerick, *ibid.*, **82**, 1362 (1960); (c) M. N. Rerick and E. L. Eliel, *ibid.*, **84**, 2356 (1962).

SCHEME II

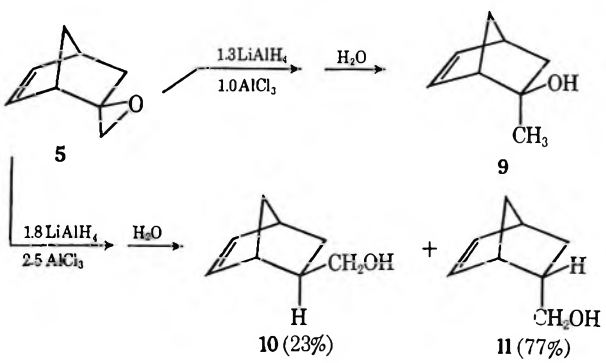


(2) to compare the relative stabilities of the intermediates, and (3) to assess the relative tendency of each intermediate to undergo attack by an external (deuteride) or internal (hydride) nucleophile with retention or inversion of configuration. The results of our investigations are reported here.

Methods and Results

Each of the terminal oxides **1**[2] and **4**–**8**[5] is reduced and/or rearranged and reduced to a mixture of known tertiary and/or primary alcohols when treated with an ethereal solution of lithium aluminum hydride and aluminum chloride. As in previously reported cases,[7] the relative amount of primary alcohol(s) formed is proportional to the relative amount of halide used. For example, at −10–0° the reaction of 30 mol % spiro[2-norbornen-*exo*-5,2′-oxacyclopropane] (**5**), with 40 mol % lithium aluminum hydride and 30 mol % anhydrous aluminum chloride produces only the tertiary alcohol, *endo*-5-methyl-2-norbornen-*exo*-5-ol (**9**),[8a] but a mixture of 19 mol % **5**, 34 mol % hydride, and 47 mol % aluminum trichloride yields only the two primary alcohols, 2-norbornene-*exo*- and -*endo*-5-methanol (**10** and **11**, respectively)[8] (Scheme III).

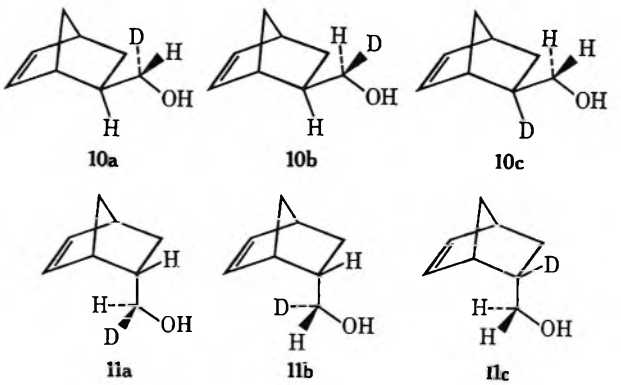
SCHEME III



Although more than one oxide/reducing agent/halide mixture was used with most of the oxides, the approximate ratio of 19:34:47 was adopted as a "standard" and each oxide was reduced in this manner. This particular mixture was chosen because it provides appreciable amounts of the primary alcohol(s) in most cases, yet differentiates the various oxides according to their tendency to undergo electrophilic rearrangement (*cf.* Experimental Section).

(8) (a) K. Alder and E. Windemuth, *Chem. Ber.*, **71**, 2409 (1938); (b) P. Resnick and J. G. Pucknat, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1959, Abstracts, p 95P; (c) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Amer. Chem. Soc.*, **83**, 3986 (1961).

When lithium aluminum deuteride is substituted for hydride in the "standard" mixture the proportions of tertiary to primary alcohols remain essentially unchanged. Under these conditions the *endo*-methanol **11** produced from the unsaturated *exo* oxide **5** appears to be monodeuterated (>95% D_1) exclusively at the α position and is composed of approximately equal amounts of the two diastereomers **11a** and **11b**. The *exo*-methanol **10** produced in this reaction consists of approximately equal amounts of the α-deuterated diastereomers **10a** and **10b**, but may also contain as much as 5% (1–2% over-all) tertiary-deuterated isomer **10c**. We can detect none of the tertiary-deuterated *endo*-methanol **11c** in the mixture.



The position and extent of the deuterium label was deduced from mass spectral and/or nmr data. For example, the 100-MHz spectrum[9] of the collected *endo*-methanol **11** exhibits doublets of similar magnitude at δ 3.24 ($J \approx 5$ Hz) and 3.06 ($J \approx 8$ Hz) which together integrate for one hydrogen, as well as a one-hydrogen multiplet at δ 2.36–2.04 due apparently to the *exo*-5 hydrogen.[10] In the spectrum of the undeuterated material these two hydrogens are found as part of a complex, ABX-type, three-proton multiplet. The α-hydrogen resonances of the deuterated *exo*-methanol **10** also appear as doublets, δ 3.63 ($J \approx 5$ Hz) and 3.45 ($J \approx 8$ Hz) in the 100-MHz nmr spectrum,[9] and together integrate for one hydrogen. In the spectrum of the *exo*-methanol, the *endo*-5-hydrogen signal (δ ≈1.6) is no longer sufficiently resolved from those of the C-6 and C-7 hydrogens (δ ≈1.0–1.5) for accurate individual integration, but it is evident from the mass spectrum of the deuterated material that this *exo* alcohol consists of 97.95% D_1 and 2.05% D_0 species.[11] Since the relative integrals of the α (area, 1) and C-5 plus C-6 plus C-7 hydrogens (area, 5) indicate that the deuterium label must be present predominately at the α position, it follows that the tertiary-deuterated species **10c** comprises less than 5% of the total product.[12]

(9) We are indebted to Dr. M. R. Wilcott, III, Department of Chemistry, University of Houston, for determining the 100-MHz spectra.

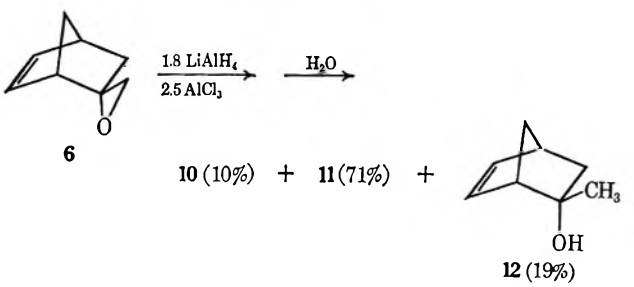
(10) *Cf.* (a) P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 2709 (1963); (b) *ibid.*, **86**, 1171 (1964); (c) S. J. Cristol, T. C. Morrill, and R. A. Sanchez, *J. Org. Chem.*, **31**, 2726 (1966).

(11) The mass spectrum was determined and interpreted by the Morgan Schaffer Corp., 5110 Courtrai Ave., Montreal 26, Quebec, Canada.

(12) An indication of the position of the deuterium label was also obtained by analysis of the mass spectrum.[11] A comparison of the relative intensities of the *m/e* 93 (P − CHDOH?) and 94 (P − CH_2OH?) fragments in the monodeuterated species with those in the mass spectrum of the nondeuterated material indicates that approximately 5% of the deuterium label is located somewhere other than at C-8 and may therefore be at C-5. However, the quantitative analysis is complicated since ions are present corresponding to P − 29, P − 30, P − 32, and P − 33. Under the circumstances we believe that the results obtained by nmr analysis are probably more reliable.

The unsaturated *endo* oxide, spiro[2-norbornen-*endo*-5,2′-oxacyclopropane] (**6**) reacts with the "standard" hydride mixture at −10–0° to produce 10% **10**, 71% **11**, and 19% tertiary alcohol *exo*-5-methyl-2-norbornen-*endo*-5-ol (**12**)[5a,13] (*e.g.*, see Scheme IV).

SCHEME IV

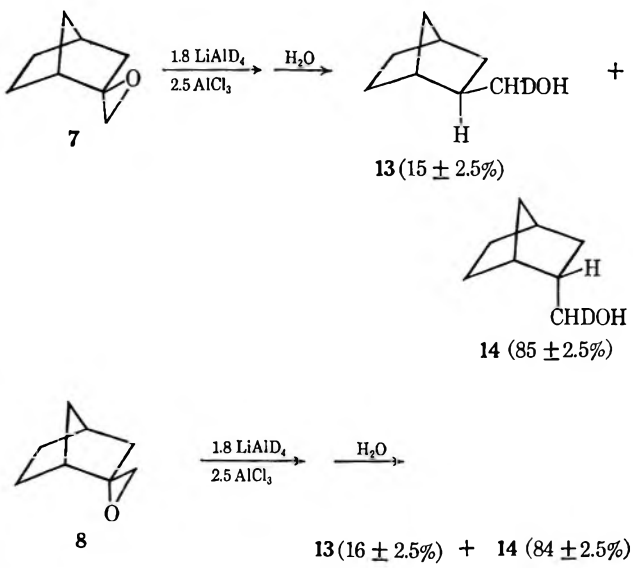


When the reductive rearrangement is repeated with "standard" lithium aluminum deuteride–aluminum trichloride, the 100-MHz nmr spectra[9] of the collected primary alcohols **10** and **11** again show no evidence of either of the tertiary-deuterated species **10c** and **11c**, although the mass spectrum[11] of the *endo*-methanol **11** indicates that it consists of 3.0% D_0, 94.5% D_1, and 2.5% D_2 species and *may* contain as much as 10% of the deuterium at C-5.[12]

When the two saturated oxides, spiro[norbornane-*exo*- and -*endo*-2,2′-oxacyclopropanes] (**7** and **8**), respectively, are reduced with the "standard" lithium aluminum deuteride–aluminum trichloride mixture they yield essentially identical mixtures of the α-deuterated norbornane-*exo*- and -*endo*-2-methanols,[14] **13** and **14** (Scheme V). Neither of the deuterated tertiary alcohols **15** or **16** could be detected by gas–liquid partition

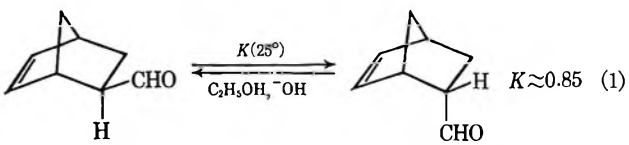
chromatographic (glpc) analysis of these mixtures, but we were able to demonstrate by control experiments using their known[13] nondeuterated counterparts that either would have been readily apparent had it been present. Although the primary alcohols were partially separated by glpc on a 300-ft Ucon-coated capillary, their relative abundance could be determined with greater precision by analysis of the 60- and 100-MHz[9] nmr spectra of the collected mixtures. The *endo*-C-3-hydrogen resonance of **14**, though split by those of the *exo*-C-2 ($J \approx 3$–4.5 Hz)[10] and *exo*-C-3 hydrogens ($J \approx 11$ Hz)[10] into a perturbed quartet centered at $\delta \sim 0.6$, is well resolved from all the other methylene hydrogen resonances of **13** and **14**. Therefore estimates of the relative proportion of these two alcohols in the mixtures were made by comparing the integral of this *endo*-C-3-hydrogen resonance in **14** with that of the combined hydroxyl–hydrogen resonances of **13** and **14**. Mass spectral analyses of the reaction mixtures[11] indicate

SCHEME V

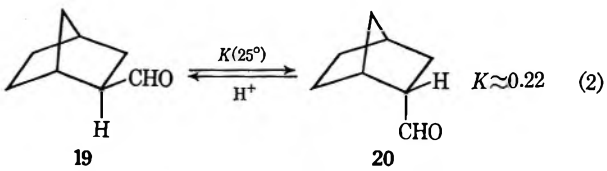


that the methanols from **7** consist of <6.6% D_0 and >93.4% D_1 species, while those from **8** contain <4.9% D_0 and >95.1% D_1. The 60-MHz nmr spectrum of each mixture reveals that the areas of the carbonyl- and hydroxyl-hydrogen resonances differ by less than 5%. Thus it follows that in each case both isomers are deuterated predominately at the carbinol carbon.

It is evident that aldehydes are not formed as intermediates during the reductive rearrangements of any of the 5,2′- or 2,2′-spiro oxides **4**–**8**. Treatment of either 2-norbornene-*exo*- or -*endo*-5-carboxaldehyde (**17** or **18**)[14] with the "standard" hydride mixture yields only the corresponding *exo*- or *endo*-methanol, **10** or **11**, respectively. Under similar conditions, a 56:44 mixture of norbornane-*exo*- and -*endo*-2-carboxaldehydes (**19** and **20**)[14] is reduced to the same ratio of the corresponding carbinols **13** and **14**. Furthermore, the epimerization of either of the unsaturated aldehydes **17** or **18** with dilute ethanolic sodium hydroxide at 25° produces an identical 54:46 mixture of *exo*/*endo*, *viz.*



while the acid-catalyzed equilibration at 25° of the two saturated aldehydes **19** and **20** yields a mixture consisting of 82% **19** and 18% **20**, *e.g.*



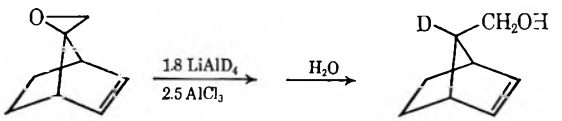
The *exo*/*endo* ratio in each of these two mixtures differs significantly from either of those observed for the carbinols formed in the reductive rearrangements of the unsaturated or saturated epoxides **5** and **6** or **7** and **8**, respectively.

In sharp contrast to the 5,2′- and 2,2′-spiro oxides **5**–**8**, which yield exclusively or predominantly α-

(13) (a) N. J. Toivonen and P. J. Mälkönen, *Suomen Kemistilehti*, *B*, **32**, 277 (1959); (b) P. Hirsjarvi and K. Salo, *ibid.*, **32**, 280 (1959); (c) P. J. Mälkönen and N. J. Toivonen, *ibid.*, **33**, 53 (1960).

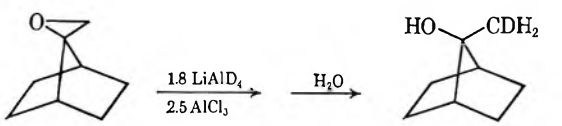
(14) For the nondeuterated compound(s), see K. Alder, G. Stein, and E. Rolland, *Ann. Chem.*, **525**, 247 (1936).

deuterated products, the 7,2′-spiro oxides **1** and **4**, react with the "standard" deuteride mixture to produce alcohols deuterated solely at the β position. Spiro[2-norbornen-*syn*-7,2′-oxacyclopropane] (**1**)[2] yields only *anti*-7-deuterio-2-norbornene-*syn*-7-methanol (**21**) as attested by the presence of a two-hydrogen singlet (due to the unsplit methylol hydrogens) at δ 3.38 in the 60-MHz spectrum of the collected product. (The spectrum of the nondeuterated alcohol exhibits a two-hydrogen doublet, J = 7 Hz, at this position.[2]) Under



1 21

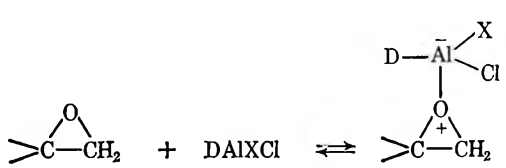
these same conditions the saturated epoxide spiro[norbornan-7,2′-oxacyclopropane] (**4**)[5b] yields a single alcohol whose glpc retention time on an 8-ft Carbowax 20M column is identical with that of authentic 7-methylnorbornan-7-ol.[2] Since the 60-MHz spectrum of the product shows no signals which can be assigned to a hydrogen α to the hydroxyl group while the mass spectrum indicates that each molecule contains a single deuterium (M^+ = 172), we conclude that this product is the primary-deuterated tertiary alcohol **22**.



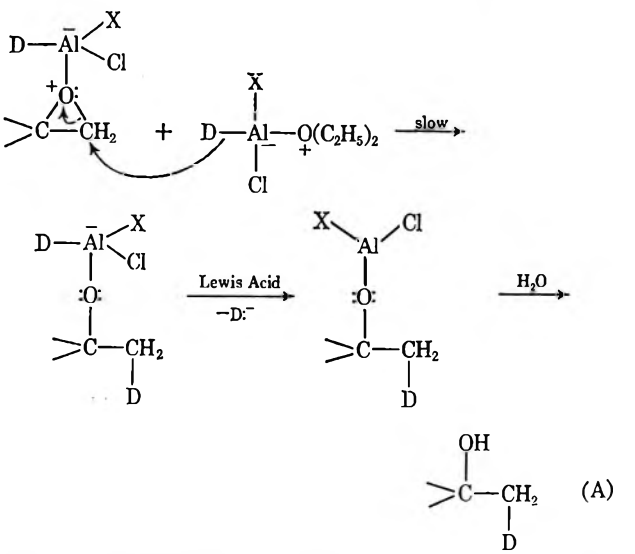
4 22

Discussion

The extensive and detailed investigations originally of Eliel, Delmonte, and Rerick[7] and recently of Ashby, Prather, Cooke, and Lott[15] have done much to define the scope and mechanistic detail of the reactions between epoxides and mixtures of lithium aluminum hydride (or deuteride) and aluminum halides. Since the reductions are invariably less facile in the absence of halide, it is likely that the initial step involves the formation of a complex between the epoxide and some electrophilic species.[15b] Ashby and Prather[15a] have demonstrated that this species in 1:1 hydride/halide mixtures is chloroalane, H_2AlCl; in 1:3 mixtures, dichloroalane, $HAlCl_2$. The reductions reported here normally utilized 1.8:2.5 mol ratios of deuteride/halide; hence the effective Lewis acid is actually a mixture of dideuteriochloroalane and deuteriodichloroalane, represented as DAlXCl where X is deuterium or chlorine. The initial step in the reaction may thus be formulated as shown below.

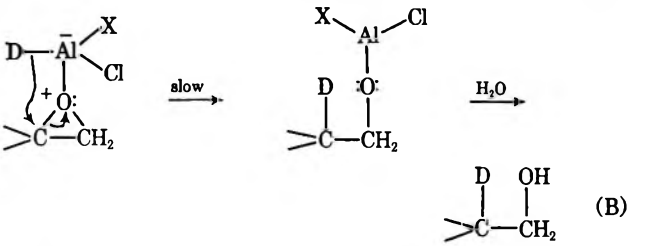


Ashby and Cooke[15b] have argued that reduction occurs directly on the undissociated complex itself when the coordinating electrophile is a relatively weak Lewis acid such as alane (AlH_3).[16] In the case of an isobutylene-type oxide, direct *inter*molecular reduction (path A) should yield a primary-deuterated tertiary alcohol predominantly. A concerted *intra*molecular



(A)

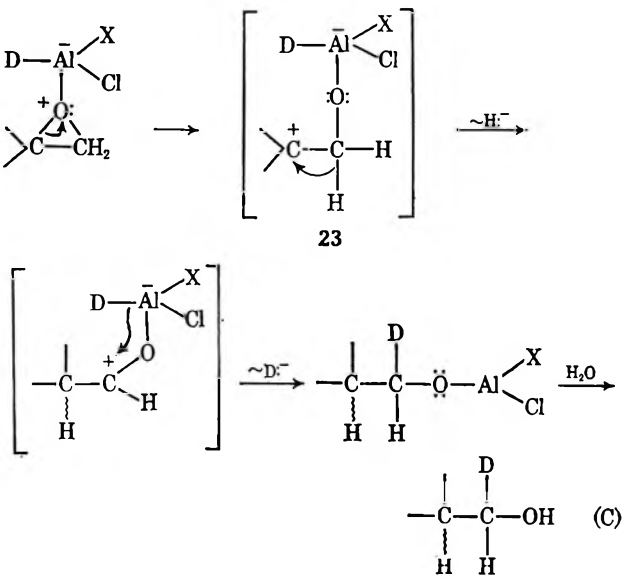
process (path B) should give a tertiary-deuterated, primary alcohol as the major product. The direct



(B)

reduction paths A and B predict that the initial configuration at the tertiary center should be retained in the products.

When a stronger Lewis acid such as dichloroalane ($HAlCl_2$) is employed, Ashby and Cooke[15b] suggest that the complex undergoes ring opening with hydrogen (or alkyl) migration prior to reduction. An isobutylene-type oxide reacting in this manner (path C) should



(C)

(15) (a) E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, **88**, 729 (1966); (b) E. C. Ashby and B. Cooke, ibid., **90**, 1625 (1968); (c) B. Cooke, E. C. Ashby, and J. Lott, *J. Org. Chem.*, **33**, 1132 (1968).

(16) Recent work of R. H. Garner, W. G. Esslinger, and G. C. Williams (153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstracts No. 0140) indicates that steric strain may also be an important factor in determining the sensitivity of the oxide ring opening to added Lewis acid.

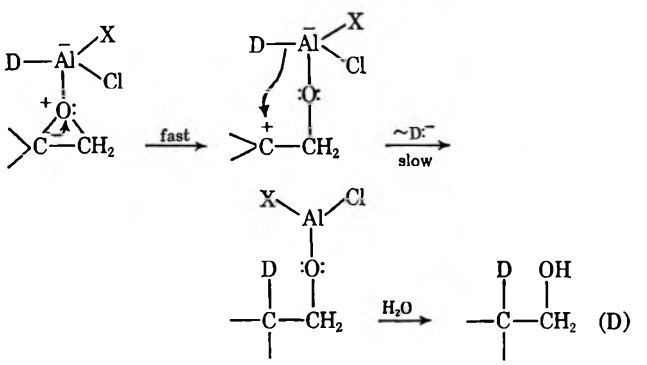
yield a primary-deuterated primary alcohol[13] predominantly or exclusively. If hydride migration is concerted with the ring opening, then the configuration at the tertiary center should be inverted in the product, but, if the free cation **23** is an intermediate, the product could be of either retained or inverted configuration.[3]

Inherent in the suggestions of Ashby and Cooke is the expectation that those epoxides which can form the most stable cations upon heterolysis will show the greatest tendency to react by the indirect route (path C). If the relative unimolecular acetolysis rates of the corresponding secondary brosylates,[17] *i.e.*

$$>\text{CHOBs} \xrightarrow[25^\circ]{\text{AcOH-AcO}^-} >\overset{+}{\text{C}}\text{—H} + \bar{\text{O}}\text{Bs}$$

can be taken as a measure of the relative stabilities of the tertiary cations (**23**), then the tendency of the spiro oxides to react by the indirect route should increase in the following order: **4** ≪ **6** < **8** < **5**, **7** < **1**.

Our data appear to confirm this prediction. Spiro[norbornan-7,2′-oxacyclopropane] (**4**) does not rearrange when treated with the "standard" hydride mixture but yields only the direct intermolecular reduction product, 7-deuteriomethyl-7-norbornanol (**22**), *via* path A. As expected, spiro[2-norbornen-*endo*-5,2′-oxacyclopropane] (**6**) exhibits a greater tendency to react in the indirect fashion and gives but 19% tertiary alcohol *exo*-5-methyl-2-norbornen-*endo*-5-ol (**12**) under these conditions. None of the other spiro oxides yields detectable amounts of such direct intermolecular reduction products. Although it is predicted to exhibit the greatest tendency for indirect reduction, spiro[2-norbornen-*anti*-7,2′-oxacyclopropane] (**1**) reacts with the lithium aluminum deuteride–aluminum trichloride mixture to produce the reduction product anticipated from the direct intramolecular path B, *viz.*, *anti*-7-deuterio-2-norbornene-*syn*-7-methanol (**21**). Since this oxide is known to rearrange in a nonconcerted fashion with retention of configuration when treated with boron trifluoride etherate[2] or when subjected to glpc on a diethylene glycol succinate or Carbowax column, it is likely that this tertiary-deuterated primary alcohol **21** actually arises *via* the nonconcerted direct intramolecular path D, shown below. Cations of the

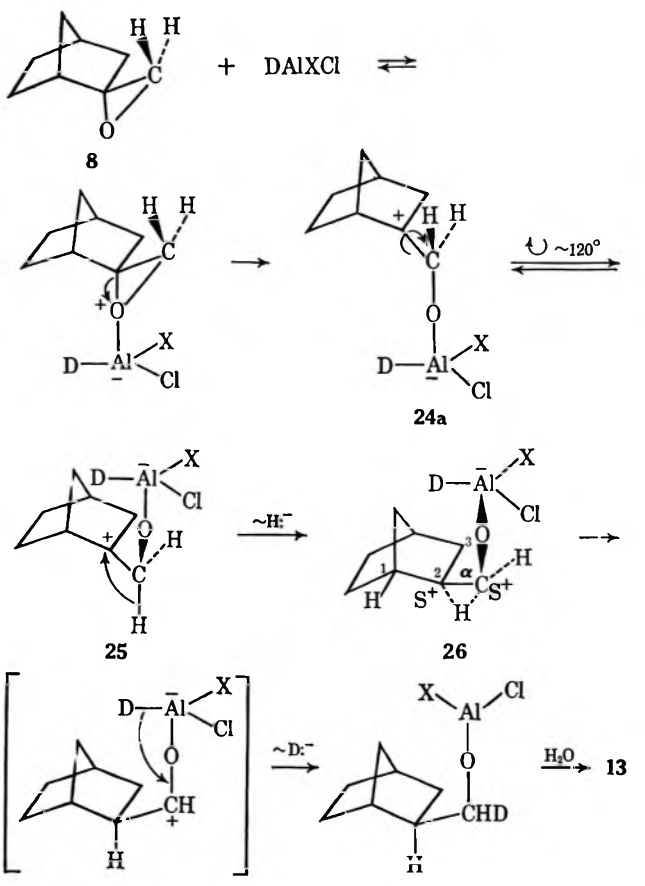


7-norbornenyl type normally react with nucleophiles at C-7 to yield products of retained configuration so that the stereochemistry of **21** is correctly predicted by either B or D.[18] The four remaining spiro oxides, **5**–**8**, react with the "standard" deuteride mixture exclusively or predominantly in the "indirect" manner, path C. Except for the relatively small amount of tertiary alcohol (**12**) produced in the case of **6**, each of these oxides yields only α-deuterated, primary alcohols.

It is not possible in most cases to specify exactly that fraction of the carbinols which is formed in a nonconcerted process by way of a cationic intermediate such as **23** (nonconcerted C), but certain limits can be placed on this possibility. For example, spiro[norbornan-*exo*-2,2′-oxacyclopropane] (**7**) yields 15% inverted product, α-deuterionorbornane-*exo*-2-methanol (**13**), and 85% **14**, which has the retained configuration at C-2. Since a concerted path would require that the product have an inverted configuration,[3] it is clear that *at least* 85% of **7** is reacting by nonconcerted C. Alternatively, since nonconcerted C could occur with retention or inversion, this path *may* constitute the exclusive mode of reduction.

In the case of the saturated *endo* oxide, **8**, we can be more precise. When treated with the "standard" lithium aluminum deuteride–aluminum chloride mixture this epoxide yields 16% **13** and 84% **14**; *i.e.*, it reacts with 16% retention and 84% inversion. A nonconcerted path is the only rational route by which the α-deuterated methanol of retained configuration, **13**, can be formed from **8**, but for this to occur it is necessary that the initial carbonium ion, **24a**, rotate ~120° about the C-2–C-α bond to give **25**, before the migrating hydride can attack the *endo* side of the ring (*e.g.*, see Scheme VI). Because this rotation is about twice as great as that required to produce **25** from **24b** (*e.g.*, see Scheme VII), it is clear that the relative

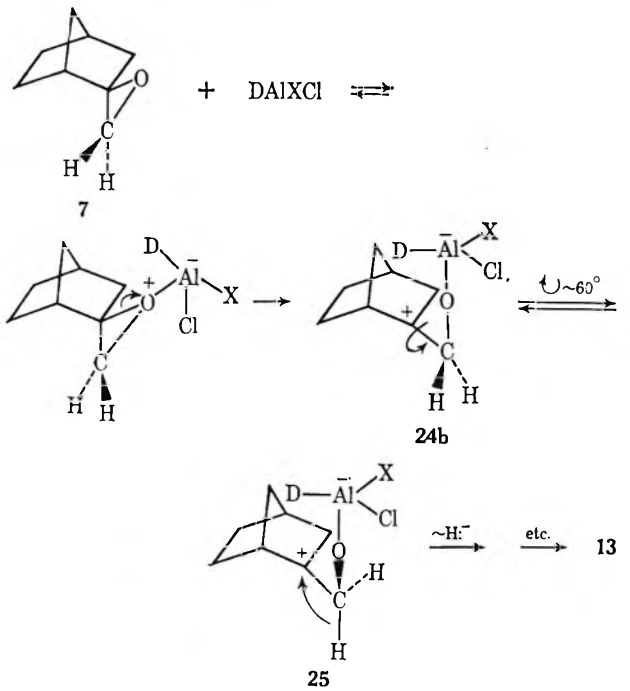
SCHEME VI



(17) *Cf.* ref 4a, p 193, and references cited therein.

(18) (a) A. Diaz, M. Brookhart, and S. Winstein, *J. Amer. Chem. Soc.*, **88**, 3133 (1966); (b) M. Brookhart, A. Diaz, and S. Winstein, *ibid.*, **88**, 3135 (1966); (c) H. Tanida, T. Tsuji, and T. Irie, *ibid.*, **88**, 864 (1966).

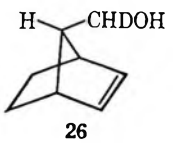
SCHEME VII



amount of **13**/**14** produced in a nonconcerted process from **8** cannot exceed the relative amount produced in a similar manner from **7**, but, even if the *exo* oxide **7** reacts *exclusively via* the nonconcerted path (C) the ratio of **13**/**14**, *i.e.*, of *endo*/*exo* hydride migration, cannot be greater than ~15:85 or 0.18. Hence, in the case of **8**, the nonconcerted path can produce no more than 15 parts of *exo*-methanol **13** for every 85 parts of *endo*-methanol **14** that are formed in this manner. Since the observed ratio of **13**/**14** is actually 14:86 in this case, it follows that within experimental error **8** *is reduced exclusively via the indirect, nonconcerted path C under these conditions.*

In a similar manner it may be concluded that *at least* 77% of the α-deuterated primary alcohols **10** and **11** from reduction of the unsaturated *exo* oxide **5** and 10% (*i.e.*, 12% of the total methanols) of those from the *endo* isomer **6** are formed in a nonconcerted manner *via* an intermediate cation such as **23** (path C). Again the possibility that **5** and **6** react exclusively by way of the nonconcerted indirect route (C) cannot be ruled out.

We have suggested that those oxides which can form stable cations by C–O cleavage ought to show a greater tendency to react in a nonconcerted fashion. Why then does **1**, which should form the most stable cation of all, not yield any hydride-migrated product, *i.e.*, the α-deuterated primary alcohol **26**? We believe that the



26

tendency of an oxide to undergo hydride migration (C) rather than deuteride transfer (D) when reduced in a nonconcerted fashion is governed by the extent of charge delocalization at the migration terminus in the intermediate cation. In the case of **1** the intermediate cation owes much of its stability to the fact that the positive charge is extensively delocalized to the C-2 and C-3 positions.[19] Hence there is little driving force for the migration of the weakly basic carbon-bonded internal nucleophile, hydride, from C-8 to C-**7**, and the more strongly basic aluminum-bonded external nucleophile, deuteride, is transferred from the coordinated deuterioalane instead. Attack is exclusively at C-**7** rather than at C-2 or C-3 as in the case of the free carbonium ion[19] because the coordinated alane, $^{+}$RO–Al^{-}DXCl, is a much stronger reducing agent (nucleophile) than is the deuterioalane–diethyl ether complex, $R_2O\rightarrow AlDXCl$.[7c] Internal nucleophilic attack (hydride migration) is the exclusive reaction when **1** is rearranged to aldehyde by treatment with boron trifluoride etherate[2] because no stronger external nucleophile is present. In the reduction of the oxides **6**–**8**, the intermediate cations are not so highly delocalized and internal neucleophilic attack (hydride migration) occurs before the external nucleophile (deuteride) can be transferred.

TABLE I

	Starting oxide			
				
	5	**6**	**7**	**8**
Ratio of *exo*/*endo* primary-deuterated methanol	0.30	0.14	0.18	0.19
Fraction of primary-deuterated methanols produced in a nonconcerted process (C)	0.77–1.0	0.12–1.0	0.85–1.0	~1.0
Ratio of *exo*/*endo* hydride attack in the nonconcerted reaction	≥3.3	3.3–7.1	≥5.7	~5.2

Of particular interest are the ratios of *exo*/*endo* hydride attack which are observed when the spiro oxides **5**–**8** are reduced in an indirect nonconcerted manner (C). These ratios may be derived in each case from the product composition and the estimated extent of nonconcerted reaction. The results are summarized in Table I.

Where a firm upper limit can be placed on the ratio of *exo*/*endo* attack in the nonconcerted process, *e.g.*, in **6** and **8**, the observed values of 3.3–7.1 and ~5.2, respectively, are much smaller than those usually found for reactions which proceed *via* tertiary norbornyl or tertiary norbornenyl cations.[20] For example, the hydrolysis of 2-methyl-*exo*-norbornyl chloride in 65% aqueous dioxane yields 170 times more 2-methyl-*exo*-2-norborneol than 2-methyl-*endo*-2-norborneol,[21] while the mild alkaline hydrolysis of 5-methyl-2-norbornen-*exo*-5-yl chloride gives "mainly" 5-methyl-2-norbornen-

(19) (a) H. C. Brown and H. M. Bell, *J. Amer. Chem Soc.*, **85**, 2324 (1963) (b) S. Winstein, A. H. Lewin, and K. C. Pande, *ibid.*, **85**, 2324 (1963).

(20) P. von R. Schleyer, *ibid.*, **89**, 699, 701 (1967), and references cited therein.

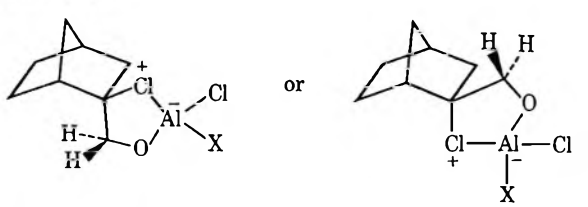
(21) H. C. Brown and H. M. Bell, *ibid.*, **86**, 5006 (1964).

exo-5-ol.[22] Even larger *exo/endo* ratios are observed when such cations react with "internal" nucleophiles: *exo,exo*-3,2-hydride or methyl shifts in these systems occur at least 300 times more rapidly than do their corresponding *endo,endo* counterparts.[23]

These large preferences for *exo* attack in norbornyl cations where charge delocalization is probably not an important factor[20,24] have been variously attributed to steric hindrance[25] or to a torsional effect between the asymmetrically placed hydrogen at C-1 and the C-2 substituent (methyl) which leads to more severe nonbonded interactions when attack is from the *endo* direction.[20] Schleyer has suggested that a torsional effect may also account for the relatively low *exo/endo* ratios that are observed in reactions which involve the formation or dissociation of exocyclic double bonds in norbornane derivatives,[20] *viz.*, reduction of dehydronorcamphor with sodium borohydride (6.2)[26] or lithium aluminum hydride (10),[27] exchange reactions of dehydronorcamphor dimethyl ketal (16),[28] and chromic acid oxidations of *exo*- and *endo*-norborneols (2.5).[29]

The relatively small preferences for *exo*-hydride attack which are observed in the nonconcerted reductions of the spiro oxides **6** and **8** could be due to either steric or torsional effects. The steric bias for *exo* attack by migrating hydride should be less here than in those cases where the nucleophile must approach the ring from a more remote position. Similarly, even though these nonconcerted reductive rearrangements clearly do not involve exocyclic double bonds, the torsional bias against *endo* attack by the internal nucleophile would also be less than for attack by an external nucleophile. The transition state for *endo* hydride migration (**26**) can be reached from the intermediate **25** with relatively little deflection (<15?) of the C-2–C-α bond from the plane of carbons 1, 2, and 3, and thus entails but a small increase in the nonbonding interaction between C-α and the bridgehead hydrogen at C-1.

If chlorine-bridged charge-transfer complexes rather than free cations are the actual product-forming intermediates, *e.g.*



then relatively low ratios of *exo/endo* attack might also be observed. Even though hydride migration should invert the configuration at C-2, there would probably be little difference in stability between the *exo* and *endo* isomers of such complexes. We doubt that chlorine bridging can be important here though for no products are observed that might be expected to result from chlorine migration, *e.g.*, chlorohydrins,[7c] tertiary-deuterated primary alcohols, or glycols.

Experimental Section[30]

2-Norbornene-*exo*- and -*endo*-5-carboxaldehydes (17 and 18).—A mixture of the isomeric aldehydes **17** (26%) and **18** (74%) was prepared by the addition of cyclopentadiene to acrolein according to the procedure for Alder and coworkers:[14] bp 61–63° (9 mm) [lit.[14] 70–72° (20 mm)]. The isomers were separated by glpc on the 8-ft Carbowax column (column temperature 150°, helium flow 30 ml/min).

The first component had retention time of 9.4 min; relative abundance 26%; ir (CCl_4) 3140, 3067, 714 (CH=CH), 2809, 2710, 1723 cm^{-1} (CHO); nmr (CCl_4) δ 9.72 [doublet, J = 2.6 Hz (1 >CHCHO)], 6.12 [asymmetric triplet (2 CH=CH)], 3.20–2.82 [two broad overlapping singlets (2 ⩾CH, bridgehead)], 2.44–1.72 [complex multiplet (1 >CHH + 1 >CHCHO)], 1.57–0.90 [complex multiplet (3 >CHH + >CHH)]; uv (isooctane) 301 mμ (ϵ 430); **semicarbazone**, mp 163.5–164°, uv (95% ethanol) 234 mμ (ϵ 16,000).

Anal. Calcd for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.13 H, 7.38; N, 23.23.

The reduction of a 57-mg (0.47 mmol) sample of the aldehyde with excess lithium aluminum hydride yielded, after collection from the 8-ft Carbowax column (column temperature 150°, helium flow 100 ml/min), 32 mg (0.26 mmol, 55%) of 2-norbornene-*exo*-5-methanol (**10**):[8] ir (CCl_4) 3629, 3339, 1028 (CH_2-OH), 3060, 708 cm^{-1} (CH=CH); nmr (CCl_4) δ 5.91 [asymmetric triplet (2 CH=CH)], 4.3 [concentration-dependent singlet (1 OH)], 3.50 [octet (2 $>CH^XCH^AH^BOH$)], 2.73 [broad multiplet (2 ⩾CH, bridgehead)], 1.86–0.90 [complex multiplet (1 $>CH^X$-CH^AH^BOH + 4 >CHH)].

The **second component** had a retention time of 11.7 min; relative abundance 74%; ir (CCl_4) 3140, 3067, 723 (CH=CH), 2811, 2715, 1729 cm^{-1} (CHO); nmr (CCl_4) δ 9.31 [doublet, J = 2.5 Hz (1 >CHCHO)], 6.02 [octet (2 CH=CH)], 3.21 [broad singlet (1 ⩾CH, bridgehead)], 3.08–2.63 [complex multiplet (1 >CH-CHO + 1 ⩾CH, bridgehead)], 2.15–1.13 [complex multiplet (4 >CHH + >CHH)]; uv (isooctane) 298 mμ (ϵ 260); **semicarbazone**, mp 160–161°, uv (95% ethanol) 233 mμ (ϵ 22,000).

Anal. Calcd for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.06; H, 7.28; N, 23.17.

Reduction of a 67-mg (0.55 mmol) sample of the second aldehyde with excess lithium aluminum hydride gave 42 mg (0.34 mmol, 62%) of 2-norbornene-*endo*-5-methanol (**11**):[8] ir (CCl_4) 3627, 3333, 1031 (CH_2OH), 3055, 721 cm^{-1} (CH=CH); nmr (CCl_4) δ 5.96 [septet (2 CH=CH), 4.43 [concentration-dependent singlet (1 OH)], 3.19 [octet (2 $>CH^XCH^AH^BOH$)], 3.0–2.6 [two broad overlapping singlets (2 ⩾CH, bridgehead)], 2.22 [multiplet (1 $>CH^XCH^AH^BOH$)], 2.0–1.1 [complex multiplet (2 >CHH + 1 >CHH, *exo*)], 0.47 [octet (1 >CHH, *endo*)].

The Epimerization of 2-Norbornene-*exo*- and -*endo*-5-carboxaldehydes (17 and 18).—To a 0.5-g sample of the mixture of **17** (26%) and **18** (74%) (*vide supra*) was added 35 ml of a 5% aqueous sodium hydroxide solution and enough 95% ethanol to render the mixture homogeneous. The solution was stirred at

(22) P. von R. Schleyer and R. E. O'Connor, 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1958, Abstracts, p 39P.

(23) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Amer. Chem. Soc.*, **87**, 3248 (1965); A. M. T. Finch, Jr., and W. R. Vaughn, *ibid.*, **87**, 5520 (1965).

(24) (a) H. C. Brown, *Chem. Brit.*, 199 (1966); (b) H. C. Brown and K. Takeuchi, *J. Amer. Chem. Soc.*, **88**, 5336 (1966).

(25) (a) H. C. Brown, "The Transition State," Special Publications of the Chemical Society, No. 16, The Chemical Society, London, 1962, p 140 ff; (b) H. C. Brown, I. Rothberg, P. von R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Natl. Acad. Sci., U. S.*, **56**, 1653 (1966).

(26) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966).

(27) R. Howe, E. C. Friedrich, and S. Winstein, *ibid.*, **87**, 379 (1965).

(28) T. G. Traylor and C. L. Perrin, *ibid.*, **88**, 4934 (1966).

(29) H. Kwart and P. S. Francis, *ibid.*, **81**, 2116 (1959).

(30) Melting and boiling points are uncorrected. Microanalyses were performed by Bernhardt Mikroanalitisches Laboratorium, 5251 Elbach über Engelskirchen, Germany. The ir spectra were determined on a Perkin-Elmer grating spectrophotometer, Model 337, the 60-MHz nmr spectra on a Varian A-60 spectrometer using tetramethylsilane (δ 0.00) and/or chloroform (δ 7.31) as internal standards, and the uv spectra on a Perkin-Elmer Model 202 spectrophotometer. The gas chromatographic analyses, uncorrected for differences in thermal conductivity of the components, were carried out in an F & M Model 500 chromatograph equipped with a hot-wire detector using either an 8 ft × 0.25 in. column packed with 20% Carbowax 20M on 60/80 mesh nonacid-washed Chromosorb W or a 12 ft × 0.25 in. column packed with 20% TCEP on 60/80 mesh nonacid-washed Chromosorb P or in an F & M Model 500 equipped with a Model 1609 flame ionization detector using a 300 ft × 0.02 in. capillary coated with water-insoluble Ucon. Preparative gas chromatography was performed on an Aerograph Autoprep Model 700-A using a 20 ft × 0.375 in. column packed with 20% Carbowax 20M on 60/80 mesh Chromosorb W. The mass spectra were determined either by the Morgan Schaffer Corp.[11,12] or on a Hitachi Model RMU-6E mass spectrometer.

room temperature and at intervals samples were withdrawn. The samples were extracted with pentane and the extracts were analyzed by glpc on the 8-ft Carbowax column (column temperature 150°, helium flow 75 ml/min). The pure aldehydes are stable to glpc under these conditions. Approximate equilibrium is apparently reached after 15–20 min at which point the mixture contains 54% unsaturated *exo* aldehyde **17** and 46% *endo* aldehyde **18**.

Norbornane-*exo*- and -*endo*-2-carboxaldehydes (19 and 20).[14]—A 7.0-g (0.057 mol) sample of mixed (26% *exo* and 74% *endo*) 2-norbornene-5-carboxaldehydes (**17** and **18**) was hydrogenated in a Parr apparatus at about 3-atm pressure using 100 mg of 5% palladium-on-carbon catalyst in an ethyl acetate solvent. The initial rapid uptake of hydrogen ceased after about 30 min. The catalyst was removed by filtration and the solvent was distilled under nitrogen at 760 mm. The residue was distilled to yield 6.0 g (0.048 mol, 85%) of product, bp 69–70° 13 mm). The *exo* and *endo* isomers were partially separated by glpc on the TCEP column at 115° using a helium flow of 100 ml/min; retention times 21.4 (minor component, **19**) and 23.4 min (major component, **20**). The nmr spectrum (CCl_4) of the mixture shows a perturbed singlet at δ 9.67 and a doublet ($J \approx 1.5$ Hz) at 9.54 due to the aldehyde hydrogens of **19** and **20**, respectively. Addition of 1 drop of 6 *N* hydrochloric acid to the sample tube results, after an induction period of ~15 min, in a simultaneous increase of the upfield and decrease of the downfield signal.

Because of the extreme ease with which they are oxidized or epimerized, no further attempt was made to isolate or characterize the individual saturated aldehydes. The mixed 2,4-dinitrophenylhydrazones melted at 147–148° (lit.[14] mp 141–142°).

The Epimerization of Norbornane-*exo*- and -*endo*-2-carboxaldehydes (19 and 20).—To a 0.5-g sample of the hydrogenated Diels–Alder mixture in 6 ml of ether was added 1 ml of 6 *N* hydrochloric acid. The reaction mixture was stirred at room temperature and at various times samples of the ethereal layer were withdrawn, dried over anhydrous sodium sulfate, and analyzed by glpc on the TCEP column (column temperature 130°, helium flow 95 ml/min). An equilibrium mixture of 82% *exo* and 18% *endo* was reached in about 25–30 hr.

An attempt to equilibrate these saturated aldehydes in the manner described for **17** and **18**, *i.e.*, using sodium hydroxide catalyst, resulted in the formation of an apparently polymeric, high-boiling material.

Norbornan-*exo*- and -*endo*-2-methanols (13 and 14).[14]—A 20:80 mixture of the unsaturated alcohols **10** and **11** (Interchemical Corp.[31]) was separated by preparative glpc on the 20-ft Carbowax column. Each of the components was hydrogenated in ethyl acetate solution using 5% palladium on carbon as catalyst. The solvent was removed by distillation at atmospheric pressure.

The *exo* isomer (**13**)[8,14] was distilled in a short-path still at 100° (3 mm): ir (CCl_4) 3624, 3323, 1038 cm^{-1} (CH_2OH); nmr (CCl_4) δ 3.26 [perturbed doublet, J = 7 Hz (2 >$CH^XCH^AH^BOH$)], 3.0 [concentration-dependent singlet (1 OH)], 2.17 [broad singlet (2 ⩾CH, bridgehead)], 1.8–0.8 [complex multiplet (8 >CHH + 1 >CH–)].

The *endo* isomer (**14**)[8,14] was distilled at 85° (10 mm): ir (CCl_4) 3627, 3340, 1051 cm^{-1} (CH_2OH); nmr (CCl_4) δ 3.47 [perturbed doublet, J = 7 Hz (2 >$CH^XCH^AH^BOH$)], 3.2 [concentration-dependent singlet (1 OH)], 2.40–0.84 [complex multiplet (2 ⩾CH, bridgehead + 6 >CHH + 1 >CHH (*exo*) + 1 >CH–)], 0.60 [broad quartet (1 >CHH *endo*)].

***endo*-2-Methylnorbornan-*exo*-2-ol (15).**[13]—An 87-mg (0.70 mmol) sample of spiro[norbornan-*exo*-2,2′-oxacyclopropane][4a] (**7**) in 5 ml of anhydrous ether was added in small portions to a stirred slurry of 61 mg (1.6 mmol) of lithium aluminum hydride in 2 ml of ether. The mixture was stirred for 30 min after the addition had been completed and was then decomposed by the addition of a few drops of 15% aqueous sodium hydroxide. The precipitated salts were washed with ether and the combined ethereal extract was dried over anhydrous magnesium sulfate. The solvent was distilled at atmospheric pressure and the residue was sublimed at 65° (65 mm) to yield 23 mg (0.18 mmol, 26%) of white needles. A glpc analysis on the 8-ft Carbowax column (column temperature 150°, helium flow 125 ml/min) showed only one peak. The ir spectrum of the product was identical with that of authentic **15**.[13]

(31) We thank the Interchemical Corp. for a generous sample of this material.

***exo*-2-Methylnorbornan-*endo*-2-ol (16)** was prepared by the reduction of spiro[norbornan-*endo*-2,2′-oxacyclopropane] (**8**)[4a] in the manner described for **15** (*vide supra*) or by the addition of methylmagnesium iodide to norcamphor.[13]

The Reduction of Epoxides with Lithium Aluminum Deuteride (or Hydride) and Aluminum Trichloride. A. Spiro[2-norbornen-*exo*- and -*endo*-5,2′-oxacyclopropanes] (5 and 6).—A slurry of 30 mg (0.79 mmol, 34 mol %) of lithium aluminum hydride and 142 mg (1.07 mmol, 47 mol %) of anhydrous aluminum chloride in 5 ml of anhydrous ether was prepared in a drybox and stirred in an ice–salt bath for 30 min. A sclution of 53 mg (0.43 mmol, 19 mol %) of epoxide **5** in 3 ml of anhydrous ether was dropped slowly into the cold, stirred slurry. The reaction mixture was stirred for an additional 30 min in the ice–salt bath and then for 60 min at room temperature. Sufficient 15% aqueous sodium hydroxide was added to decompose the complex. The ethereal solution was decanted from the precipitated salts which were washed thoroughly with ether. The combined ethereal solution was dried over anhydrous magnesium sulfate, filtered, and concentrated to about 0.5 ml by distillation of the solvent at atmospheric pressure. Analysis by glpc on the 8-ft Carbowax column (column temperature 150°, helium flow 70 ml/min) showed two components which were identified as 2-norbornene-*exo*-5-methanol (**10**, 23%) and 2-norbornene-*endo*-5-methanol (**11**, 77%) by glpc collection (over-all yield 30 mg, 0.24 mmol, 56%) and comparison with authentic samples. No unreacted starting material, aldehyde, or tertiary alcohol **9** could be detected in the reaction mixture.

When the composition of the reactants was changed to 97 mg (0.79 mmol, 30 mol %) of epoxide **5**, 146 mg (1.09 mmol, 40 mol %) of aluminum chloride, and 30 mg (0.79 mmol, 30 mol %) of lithium aluminum hydride, only one product, identical in all respects with authentic *endo*-5-methyl-2-norbornen-*exo*-5-ol (**9**),[4a] was obtained.

The reaction was also carried out using 81 mg (0.66 mmol, 19 mol %) of **5**, 219 mg (1.64 mmol, 45 mol %) of aluminum chloride, and 55 mg (1.31 mmol, 36 mol %) of lithium aluminum deuteride. Glpc analysis on the 8-ft Carbowax column at 150° and a helium flow of 67 ml/min showed two products with retention times of 17.0 and 20.7 min, identical with those of authentic **11** and **10**, respectively. The products were separated by glpc and the position of the deuterium label was determined by analysis of their 100-MHz nmr spectra. The nmr spectrum of the *endo* isomer had signals at δ 5.96 [octet (2 CH=CH)], 3.4 [concentration-dependent singlet (1 OH)], 3.24 [doublet, $J \approx 5$ Hz (~½ >CHCHDO)], 3.06 [doublet, $J \approx 8$ Hz (~½ >CHCDHO)], 2.88 [broad singlet (1 ⩾CH, bridgehead)], 2.72 [broad singlet (1 ⩾CH, bridgehead)], ~2.20 {broad multiplet [1 >CH(CHD)O]}, 2.0–1.1 [complex multiplet (2 >CHH + 1 >CHH, *exo*)], 0.46 [octet (?) (1 >CHH, *endo*)]; the mass spectrum[11] showed M⁺ = 125. We conclude that this product is a mixture of the α-deuterated alcohols **11a** and **11b**. The nmr spectrum of the *exo* isomer has signals at δ 6.04 [multiplet (2 CH=CH)], 3.63 [perturbed doublet, $J \sim 5$ Hz (~½ >CHCHDO)], 3.45 [perturbed doublet, $J \sim 8$ Hz (~½ >CHCDHO)], 2.78 [broad singlet (2 ⩾CH, bridgehead)], 2.6 [concentration-dependent singlet (1 OH)], 1.8–1.0 [complex multiplet (4 >CHH + 1 >CH–)]; the mass spectrum[11] showed M⁺ (relative abundance) = 124 (2.05%), 125 (97.95%). We conclude that this product is a mixture of the α-deuterated alcohols **10a** and **10b**.

A sample of 54 mg (0.44 mmol, 18 mol %) of the epoxide **6** was reduced in ether solution with a mixture of 155 mg (1.17 mmol, 49 mol %) of aluminum chloride and 30 mg (0.79 mmol, 33 mol %) of lithium aluminum hydride in the manner described for the isomeric oxide **5**. Glpc analysis on the 8-ft Carbowax column showed three components. The products were collected (combined yield 38 mg, 70%) and identified by comparison with authentic samples as the tertiary alcohol **12** (19%) and the primary alcohols **10** (10%) and **11** (71%). The reduction of **6** was repeated using 90 mg (0.74 mmol, 19 mol %) of the epoxide, 243 mg (1.87 mmol, 46 mol %) of aluminum chloride, and 60 mg (1.42 mmol, 35 mol %) of lithium aluminum deuteride. The primary alcohols were separated on the 8-ft Carbowax column. The 100-MHz nmr spectra of the *exo* and *endo* isomers were identical with those of **10a** plus **10b** and **11a** plus **11b**, respectively, obtained in the reduction of epoxide **5**. From the mass spectrum of the *endo* isomer it was calculated[11] that M⁺ (relative abundance) = 124 (3.0%), 125 (94.5%), 126 (2.5%).

B. Spiro[norbornan-*exo*- and -*endo*-2,2′-oxacyclopropanes] (7 and 8).—The reaction of 103 mg (0.82 mmol, 19 mol %) of the

oxide **7** with 271 mg (2.04 mmol, 47 mol %) of aluminum chloride and 62 mg (1.47 mmol, 34 mol %) of lithium aluminum deuteride as described for **5** gave, after collection from the 8-ft Carbowax column (column temperature 150°, helium flow 125 ml/min), 63 mg (0.50 mmol, 60%) of product which appeared as a single peak, retention time 16.8 min. On a capillary Ucon column at 95° (N_2 at 18 psi) two broad poorly resolved peaks are evident whose retention times, 53 and 55 min, are identical with those of the authetic primary alcohols **14** and **13**, respectively. No tertiary alcohols (**15** and **16**) were found even though mixed glpc with authentic samples indicates that they would have been separated under our analysis conditions. The proportion of *exo/endo* isomers and the position of the deuterium label was estimated from the 100-MHz and 60-MHz nmr spectra of the collected mixture: δ ~3.4 [broad poorly resolved multiplet (1 >CHCHDO)], 2.8 [concentration-dependent singlet (1 OH)], 2.23–1.98 [broad multiplet (2 >CH, bridgehead?)], 1.98–0.80 [complex multiplet (6 >CHH + 1 >CHH, *exo*, + 1 >CH– + <1 >CHH, *endo*], 0.60 [octet (<1 >CHH, *endo*)]. The ratio of the areas of the signals at δ 3.4, 2.8, and 0.6 is estimated to be 1.0:1.0:0.85 (accurate to ~5%). The mass spectrum[11] showed $M^+ - 18$[32] (relative abundance) = 108 (≤4.9%), 109 (≥95.1%). From these measurements we conclude that essentially all of the deuterium is in the α position and that the isomeric primary alcohols **14** and **13** are present in the proportion of 15:85.

The oxide **8** was reduced in a similar manner using 54 mg (0.44 mmol, 19 mol %) of the epoxide, 152 mg (1.14 mmol, 47 mol %) of aluminum chloride, and 33 mg (0.76 mmol, 34 mol %) of lithium aluminum deuteride. Collection from the 8-ft Carbowax column gave 38 mg (68%) of primary alcohol(s). No tertiary alcohol could be detected by glpc. Analysis of the nmr spectrum indicates that virtually all of the product is α deuterated and that it consists of ~84% **14** and ~16% **13**. The mass spectrum[11] showed $M^+ - 18$[32] (relative abundance) = 108 (≤6.6%), 109 (≥93.4%).

C. Spiro[2-norbornen-*anti*-7,2′-oxacyclopropane] (1).—The reaction of 230 mg (1.89 mmol, 19 mol %) of **1** with 617 mg (4.63 mmol, 47 mol %) of aluminum chloride and 140 mg (3.34 mmol, 34 mol %) of lithium aluminum deuteride in the manner described in part A yielded 207 mg (72%) of distilled product.[2] Glpc analysis on the 8-ft Carbowax column showed the presence of a single component: nmr (CCl_4) δ 5.83 [triplet (2 CH=CH)], 3.38 [singlet (2 >CDCH$_2$O)], 3.1 [broad concentration-dependent singlet (1 OH)], 2.73 [multiplet (2 >CH, bridgehead)], 1.9–0.8 [complex multiplet (4 >CHH)]. We conclude that the product is the tertiary-deuterated primary alcohol **21**. When the experiment was repeated using 946 mg (7.75 mmol, 47 mol %) of epoxide **1**, 530 mg (4.01 mmol, 24 mol %) of aluminum chloride, and 200 mg (4.76 mmol, 29 mol %) of lithium aluminum deuteride, alcohol **21** was again the only product obtained.

D. Spiro[norbornan-7,2′-oxacyclopropane] (4).—The reaction of 348 mg (2.80 mmol, 19 mol %) of epoxide **4** with 215 mg (5.13 mmol, 34 mol %) of lithium aluminum deuteride and 919 mg (6.88 mmol, 47 mol %) of aluminum chloride gave, after sublimation [80° (50 mm)], 286 mg (80%) of a single alcohol. The retention time of the product on the 8-ft Carbowax column at 100° was identical with that of authentic 7-methylnorbornan-7-ol.[2] The nmr spectrum was too complex and insufficiently resolved for detailed analysis but showed no signals which could be attributed to a methylol-type hydrogen. The mass spectrum showed M^+ (relative abundance) = 126 (≤2.0%), 127 (≥98.0%). Although our data do not permit an unambiguous assignment of the position of the deuterium label, we believe that the product is the primary-deuterated tertiary alcohol **22**.

The Reduction of Aldehydes with Lithium Aluminum Hydride–Aluminum Chloride. A. 2-Norbornen-*exo*- and -*endo*-5-carboxaldehydes (17 and 18).—Samples of 53 mg (0.43 mmol) of aldehydes **17** and **18** were each reduced in ether solution with mixtures of 30 mg (0.79 mmol) of lithium aluminum hydride and 150 mg (1.13 mmol) of aluminum chloride as described for the epoxides (*cf.* epoxide **5**). The products were identified by comparison of their glpc retention times and ir spectra with those of authentic samples. Each of the aldehydes was found to give only one product, the corresponding primary alcohol **10** or **11**, respectively.

B. Norbornane-*exo*- and -*endo*-5-carboxaldehydes (19 and 20).—A mixture of **19** (56%) and **20** (44%) was reduced in the usual manner using 1.28 g (10.3 mmol) of the aldehydes, 0.76 g (19 mmol) of lithium aluminum hydride, and 3.25 g (25.6 mmol) of aluminum chloride. After work-up and distillation in a modified Hickmann still [90° (3 mm)], 1.08 g (8.25 mmol, 83%) of a product mixture was obtained whose composition was determined by analysis of the 60-MHz nmr spectrum. A comparison of the integrated areas of the methylol doublets at δ 3.26 and 3.47 showed the distillate to consist of 56% *exo* alcohol **13** and 44% *endo* alcohol **14**.

Registry No.—**10a**, 19926-82-0; **10b**, 19926-83-1; **11a**, 19926-84-2; **11b**, 19926-85-3; **13**, 19926-86-4; **14**, 19926-87-5; **17**, 19926-88-6; **17** (semicarbazone), 19926-89-7; **18**, 19926-90-0; **18** (semicarbazone), 19926-91-1; **21**, 19926-92-2.

Acknowledgments.—It is a pleasure to acknowledge the generous support given this work since its inception by the Petroleum Research Fund administered by the American Chemical Society, Grant No. 911-A4, and an institutional grant from the National Science Foundation for the purchase of a mass spectrometer.

(32) The parent ion was too weak to calculate the isotopic distribution. The calculation was therefore performed on the ion corresponding to P – H_2O making the assumption that no 1,1 elimination of water had taken place.

The Pyrolytic Rearrangement of Two Cyclobutene Epoxides[1,2]

DAVID L. GARIN

Department of Chemistry, University of Missouri–St. Louis, St. Louis, Missouri 63121

Received October 16, 1968

The pyrolytic rearrangement of *exo*-bicyclo[3.2.0]hept-6-ene oxide (1) and *exo*-bicyclo[4.2.0]oct-7-ene oxide (6) have been investigated. At 420°, the former gives Δ^2-cyclopentenylacetaldehyde (2) in 50% yield. At 400°, the latter gives Δ^2-cyclohexenylacetaldehyde (7), 1-methylcyclohexene, and 3,4-tetramethylene-2,3-dihydrofuran (8). The corresponding cyclobutanones (10 and 11) were shown not to be intermediates. The structures of the products have been assigned on the basis of comparison with authentic samples and further chemical transformations.

There are many examples of the pyrolytic rearrangement of epoxides in the literature.[3,4] To our knowledge, there are but two reports on the pyrolysis of cyclobutene epoxides.[5] In the light of recent reports on the anomolous behavior of cyclobutene epoxides with regard to attack by various nucleophiles[6-9] and rearrangements caused by Lewis acids[9-11] the results of our work on the pyrolysis of *exo*-bicyclo[3.2.0]hept-6-ene oxide (1) and *exo*-bicyclo[4.2.0]oct-7-ene oxide (6) should be of some interest[12] (Scheme I).

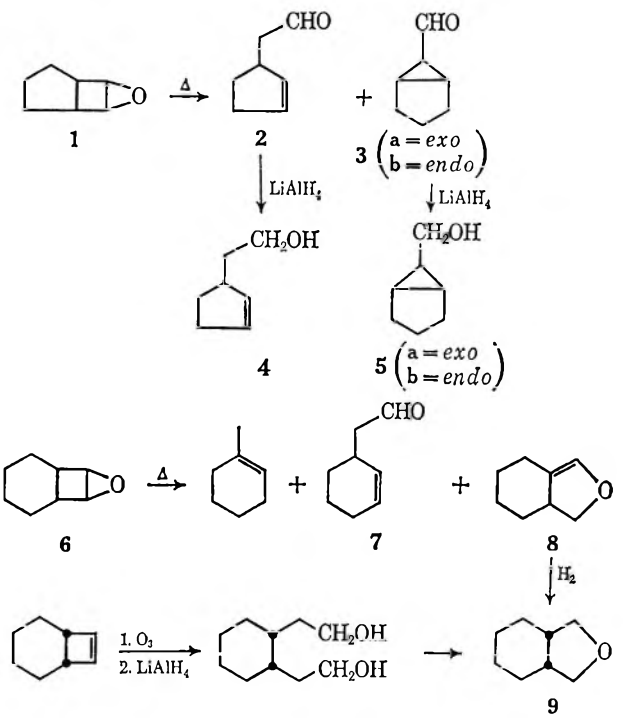
Pyrolysis was affected by dropwise addition of the epoxide to a 12-in. vertical column of glass helices in a temperature-controlled oven under slow nitrogen flow. Optimum temperatures were considered to be those that gave complete conversion of the epoxide with the lowest number of products as determined by vapor phase chromatography.

Results

Pyrolysis of 1 at 420° gives a large number of high- and low-boiling products. A sample of the major constituent of the pyrolysate (50%) was isolated by preparative vpc. Analysis of its infrared and nmr spectra suggested Δ^2-cyclopentenylacetaldehyde (2) which was verified by comparison with an authentic sample and by reduction to the corresponding alcohol and comparison with 2-(Δ^2-cyclopentenyl)ethanol (4).

One of the minor products from the pyrolysate (5%) was isolated in impure form. The nmr spectrum showed a sharp aldehyde doublet at 9.2 ppm (J = 5 cps), no olefinic protons, and a methylene region that extended to 1.0 ppm. It seemed possible that the major substituent of this mixture was bicyclo[3.1.0]-hexane-6-carboxaldehyde (3), either *exo* or *endo* or a mixture of both. The mixture was reduced with

SCHEME I



lithium aluminum hydride to the more stable alcohols. *exo*- and *endo*-bicyclo[3.1.0]hexane-6-methanols (**5a, b**) were synthesized for comparison.[13] The alcohols were analyzed by vpc on a THEED column at 125°.[14] Under these conditions, both *exo* and *endo* alcohols can be resolved. The major product from the reduction of the aldehyde (obtained from the pyrolysis of 1) was shown to be the *exo* isomer by comparison of retention times. The *endo* alcohol (**5b**) was not present. Samples of these alcohols were collected by preparative vpc. The infrared spectrum of the reduced aldehyde was superimposable with that of the authentic *exo* alcohol (**5a**) and differed from that of the *endo* alcohol (**5b**). Therefore, the aldehyde obtained from the pyrolysis of 1 is *exo*-bicyclo[3.1.0]hexane-6-carboxaldehyde (**3a**). The nmr spectrum of **5a** shows a hydroxymethylene doublet at 3.3 ppm (J = 7 cps); that of **5b** shows a hydroxymethylene doublet at 3.5 ppm (J = 7 cps).

Another minor product (2%), collected by preparative vpc, appeared to be an unsaturated ether (infrared spectrum: 3050, 1653, 1640, 1460, 1130, and 1028 cm^{-1}) but sufficient material could not be obtained to further characterize it.

(1) Presented in part at the Midwest Regional American Chemical Society Meeting, Columbia, Mo., Nov 1967.

(2) Portions of this manuscript were abstracted from the Ph.D. thesis of D. L. Garin, Iowa State University, 1964.

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

(4) An extensive review of epoxide chemistry can be found: A. Rosowsky, "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 1, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 1–523.

(5) G. Maier, *Chem. Ber.*, **96**, 2238 (1963); E. E. van Tamelen and D. Carty, *J. Amer. Chem. Soc.*, **89**, 3922 (1967).

(6) A. C. Cope and R. W. Gleason, *ibid.*, **84**, 1928 (1962).

(7) L. A. Paquette, A. A. Youssef, and M. L. Wise, *ibid.*, **89**, 5246 (1967).

(8) A. Padwa, *ibid.*, **87**, 4205 (1965).

(9) W. R. Moore and C. H. Beede, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., 1963, p 11M.

(10) J. L. Ripoll and J. M. Conia, *Tetrahedron Lett.*, 979 (1965).

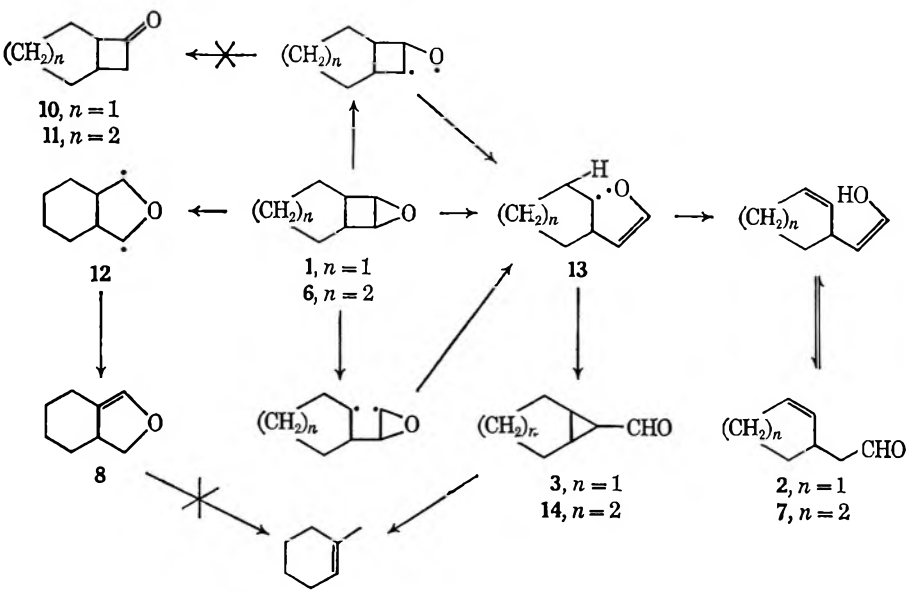
(11) J. L. Ripoll and J. M. Conia, *Bull Soc. Chim. Fr.*, 2755 (1965).

(12) Epoxides **1** and **6** were prepared by peracid oxidation of the corresponding olefins. Cope and Gleason[6] reported that the peracid oxidation of bicyclo[4.2.0]oct-7-ene gives both *exo* and *endo* epoxides with the *exo* isomer favored 87:13. The more rigid bicyclo[3.2.0]hept-6-ene would be expected to give an even greater predominance of the *exo* epoxide.

(13) K. B. Wiberg and A. J. Ashe, III, *J. Amer. Chem. Soc.*, **90**, 63 (1968).

(14) This is a 1-m, 0.25-in. diameter glass column utilizing tetrahydroxyethylenediamine (THEED) 1:3 on 60–80 firebrick. Retention times (min) at 125°: **5a**, 4.0; **5b**, 4.8.

SCHEME II



By comparison with **1**, the pyrolysis of **6** at 400° was extremely clean giving three products which were separated and collected by preparative vpc. The low-boiling product (13%) was shown to be 1-methylcyclohexene by comparison with a prepared sample. The lesser of the two major products (31%) was identified as Δ^2-cyclohexenylacetaldehyde (**7**). The infrared and nmr spectra were consistent with this structure (aldehydic proton at 9.7 ppm, t, J = 2 cps; two olefinic protons at 5.5 ppm, multiplet). The 2,4-dinitrophenylhydrazone had mp 99.5–100° (lit.[15] mp 97°). Absorption of 1 mol of hydrogen gave cyclohexylacetaldehyde identified by its 2,4-dinitrophenylhydrazone derivative which had mp 123.5–125° (lit.[16] mp 124–125°). To distinguish between the Δ^2 and possible Δ^3 isomer, the aldehyde was reduced to the corresponding alcohol with lithium aluminum hydride and compared with authentic samples of 2-(Δ^3-cyclohexenyl)ethanol[17] and 2-(Δ^2-cyclohexenyl)ethanol.[18] Though similar, the infrared spectra of the two isomers differed in the fingerprint region. The infrared spectrum of the reduced aldehyde was identical with that of the Δ^2 isomer.

Unexpectedly, the major component of the pyrolysate (56%) appeared to be an enol ether. The infrared spectrum showed absorption at 1670, 1040, 920, and 835 cm^{-1}; the ultraviolet spectrum had λ_{max} 214 mμ (ϵ 6100) in 95% ethanol. Hydrogenation in ethyl acetate with 5% platinum oxide on carbon gave a single ether which was shown to be *cis*-hexahydrophthalan (**9**) by comparison with a sample synthesized from *cis*-bicyclo[4.2.0]oct-7-ene *via* ozonolysis,[19] reduction to *cis*-hexahydrophthalyl alcohol, and dehydration.[20,21] The infrared and nmr spectra of the dihydro enol ether were superimposable with those of **9**. Thus, the enol ether is 3,4-tetramethylene-2,3-dihydrofuran (**8**).

The pyrolysis of **6** at 400° (as well as **1** at 420°) repeatedly gave the same products in the same ratio. Pyrolysis on a column packed with glass wool (greater surface area) gave the same results as pyrolysis on glass helices. A similar lack of surface effects in epoxide pyrolyses has been reported.[22] Pyrolysis of **6** at lower temperature (350°) gives only 75% conversion of the epoxide with a smaller percentage of low-boiling product. Pyrolysis at higher temperature (450°) gives less of the two major products, several low-boiling products in higher yield, and other trace products. Pyrolysis at 500° gives much polymeric material.

Discussion

Schematically, it appears that the rearrangement to the aldehydes is occurring *via* initial breakage of either the C–O epoxide bond followed by breakage of the appropriate C–C bond of the cyclobutane ring, or *vice versa*. In Scheme II, homolytic bond cleavage is shown but the transformation could also be represented by heterolytic cleavage. The diradical intermediate **13** (n = 1) can account for the formation of **3**, closing to the thermodynamically more stable *exo* isomer. The formation of the enol ether **8** is best represented by the cleavage of the C–C cyclobutanoxide bond to give the diradical intermediate **12** followed by two 1,2-hydrogen (or hydride) shifts or a 1,3-hydrogen shift. The apparent lability of this bond has been previously demonstrated.[6,7] The competitive nature of hydride shifts following the cleavage of a strained cyclobutane bond has been reported; *e.g.*, the bromination of bicyclo[2.1.0]-pentane gives mainly *trans*-1,2-dibromocyclopentane.[23]

By analogy to other cycloalkene epoxides, the cyclobutene epoxides could rearrange to carbonyl compounds forming the corresponding cyclobutanone or a cyclopropanecarboxaldehyde (by ring contraction).[1,2] The possibility that the cyclobutanones were intermediates

(15) C. W. Whitehead, J. T. Traverso, H. R. Sullivan, and F. J. Marshall, *J. Org. Chem.*, **26**, 2814 (1961).

(16) J. Fried and R. C. Elderfield *ibid.*, **6**, 566 (1941).

(17) A sample was kindly supplied by the General Electric Research Laboratories, Schenectady, N. Y.

(18) This alcohol was obtained by reduction of the known Δ^2-cyclohexenylacetic acid: W von E. Doering, E. T. Fossel, and R. L. Kaye, *Tetrahedron*, **21**, 25 (1965).

(19) J. L. Warnell and R. L. Shriner, *J. Amer. Chem. Soc.*, **79**, 3165 (1957).

(20) W. J. Bailey and H. R. Golden, *ibid.*, **75**, 4780 (1953).

(21) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, **19**, 1449 (1954).

(22) C. K. Johnson, B. Dominy, and W. Reusch, *J. Amer. Chem. Soc.*, **85**, 3894 (1963).

(23) R. T. LaLonde, *ibid.*, **87**, 4217 (1965).

which further rearranged to products was eliminated by experiment. Bicyclo[4.2.0]octan-7-one (**11**) was prepared from bicyclo[4.2.0]oct-7-ene *via* the procedure of Brown and Garg.[24] Pyrolysis in the manner described for **6** gave a gas (assumed to be ketene) and cyclohexene as the only products. In a similar fashion, bicyclo[3.2.0]heptan-6-one (**10**) gave a gas and cyclopentene as the only products. This is analogous to the pyrolysis of cyclobutanone itself which is reported to give ketene and ethylene.[25]

The enol ether **8** was investigated as a possible source of 1-methylcyclohexene since dihydrofuran is reported to pyrolytically decompose to propene and carbon monoxide.[26] The pyrolysis of **8**, under reaction conditions similar to the pyrolysis of **6** but at slightly higher temperature (420°), gave a pyrolysate which was essentially unreacted enol ether. The unobserved cyclopropanecarboxaldehyde **14** may not be stable under reaction conditions and could be the source of the 1-methylcyclohexene. Cyclopropanecarboxaldehyde itself is known to rearrange pyrolytically to propene and carbon monoxide.[26] However, the injection of **14** (*exo* isomer)[27] into a gas chromatograph with the injection port heated to 475° produced no observable decomposition.

Both heat and Lewis acids can cause an epoxide to rearrange often giving identical products in different ratios.[1,2] It is interesting to note that the reaction of **6** with LiI gives **14** but no enol ether.[27,27a]

Experimental Section[28]

***exo*-Bicyclo[3.2.0]hept-6-ene Oxide (1).**—The perbenzoic acid oxidation of bicyclo[3.2.0]hept-6-ene[29] (5.3 g, 0.056 mol) gave 4.0 g (65%) of colorless liquid, bp 61–62° (24 mm) [lit.[7] bp 84–85° (73 mm)]. Vpc analysis indicated the presence of only one component.

***exo*-Bicyclo[4.2.0]oct-7-ene Oxide (6).**—Following the epoxidation procedure of Korach, Nielsen, and Rideout,[30] bicyclo[4.2.0]-oct-7-ene[31] (8.3 g, 0.077 mol) was treated with 18 g of 40% peracetic acid solution[32] (0.095 mol) to give 4.1 g (43%) of colorless liquid: bp 71–73° (16 mm) [lit.[6] bp 82–84.5° (26 mm)]; infrared (neat), 3040, 942, 825, 809, and 760 cm^{-1}.

Pyrolysis of Liquid Epoxides and Ketones.—The liquid epoxide or ketone was drawn into a long-needle syringe. The needle was then inserted through a septum at the top of a vertical pyrolysis column. Twelve inches of the column were filled with 1/8-in. glass helices and encased in an oven maintained at 420° for **1** and **10** and 400° for **6** and **11**. The temperature was determined by attaching an iron–constantan thermocouple to the column and to a Rubicon potentiometer with reference temperature at 0°. The epoxide or ketone was allowed to drip onto the column at a slow enough rate to prevent flooding (10–15 drops/min). The system was kept under a positive nitrogen pressure. The pyrolysate was trapped in a receiver kept at −70° (Dry Ice–acetone). Pyrolysate mixtures were separated and collected by vpc utilizing a Perkin-Elmer RX column at 75–150°.[28]

Δ^2-Cyclopentenylacetaldehyde (2).—The major product from the pyrolysis of **1** displayed the following physical data: infrared (CCl_4), 3080, 2820, 2720, 1725, 1615, and 910 cm^{-1}; $\delta_{TMS}^{CCl_4}$ (in ppm) 9.7 (t, 1 H, J = 2 cps, CH_2CHO), 5.7 (multiplet, 2 H, =CH–), 3.05 (multiplet, 1 H, C=CCH<), integrates for ten total protons relative to two protons at 5.7 ppm. The infrared and nmr spectra were identical with that of an authentic sample obtained from the photolysis of norcamphor.[27,33] The 2,4-dinitrophenylhydrazone had mp 104–105° (lit.[34] mp 101–103°). A mixture melting point with the 2,4-dinitrophenylhydrazone of Δ^2-cyclopentenylacetaldehyde had mp 103–105°.

2-(Δ^2-Cyclopentenyl)ethanol (4) by the $LiAlH_4$ Reduction of 2.—**2** (250 mg), obtained from the pyrolysis of **1**, was treated with lithium aluminum hydride in ether. Distillation, *in vacuo*, in a microdistillation apparatus gave 150 mg of a pure colorless liquid which displayed the following physical data: infrared (CCl_4), 3670, 3350, 3080, 1615, 1055, 970, and 910 cm^{-1}; $\delta_{TMS}^{CCl_4}$ (in ppm) 5.6 (multiplet, 2 H, =CH–), 3.6 (t, 2 H, J = 6.7 cps, CH_2-CH_2OH), integrates for twelve protons relative to two protons at 3.6 ppm. The infrared and nmr spectra were superimposable with those of known 2-(Δ^2-cyclopentenyl)ethanol prepared by the lithium aluminum hydride reduction of Δ^2-cyclopentenylacetic acid.[35] The α-naphthylurethan of the reduced aldehyde had mp 81–83° which showed no depression upon admixture with an authentic sample of the α-naphthylurethan of **4**.

2-(Δ^2-Cyclopentenyl)ethanol (4) by the $LiAlH_4$ Reduction of Δ^2-Cyclopentenylacetic Acid.—To a stirred slurry of 0.50 g of lithium aluminum hydride in 50 ml of ether was added 1.0 g of Δ^2-cyclopentenylacetic acid.[35] After several hours, the excess hydride was quenched with a saturated aqueous solution of sodium sulfate. Hydrochloric acid (2 N) was added to hydrolyze the complex. The reaction mixture was filtered, and the ether layer was separated and dried (Na_2SO_4). Evaporation of the ether left 0.90 g of a viscous liquid. Analysis by vpc showed one product and some unreacted acid. A sample of the alcohol was collected from the gas chromatograph. Infrared and nmr spectra data are listed above.

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.83; H, 11.09.

The α-naphthylurethan had mp 82–83°.

Anal. Calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.00; H, 7.00; N, 5.25.

1-Methylcyclohexene.—The infrared spectrum of the olefin collected from the pyrolysis of **6** was found to be identical with that of authentic 1-methylcyclohexene, obtained by methyl Grignard addition to cyclohexanone and acid dehydration of the resulting alcohol.

Δ^2-Cyclohexenylacetaldehyde (7).—The lesser of the two major products from the pyrolysis of **6** displayed the following physical data: infrared (CCl_4) 3030, 2860, 2710, 1725, 1685, 1650, 1435, and 835 cm^{-1}; $\delta_{TMS}^{CCl_4}$ (in ppm) 9.7 (t, 1 H, J = 2 cps, CH_2CHO), 5.5 (m, 2 H, =CH–). The 2,4-dinitrophenylhydrazone had mp 99.5–100.5° (lit.[15] mp 97°).

Anal. Calcd for $C_{14}H_{16}O_4N_4$: C, 55.25; H, 5.30. Found: C, 55.18; H, 5.06.

Hydrogenation of 50 mg of **7** with 5% palladium on charcoal gave a compound whose 2,4-dinitrophenylhydrazone had mp 123.5–125° (lit.[16] mp 124–125° for the 2,4-dinitrophenylhydrazone of cyclohexylacetaldehyde).

Reduction of 7.—To a stirred slurry of 0.10 g of lithium aluminum hydride in 10 ml of ether was added a solution of 0.10 g of **7** in 5 ml of ether. A small amount of the resulting alcohol was collected from the gas chromatograph for spectral analysis. The infrared spectrum of this alcohol was compared with that of known 2-(Δ^3-cyclohexenyl)ethanol[17] and 2-(Δ^2-cyclohexenyl)ethanol and found to be identical with that of the latter.

2-(Δ^2-Cyclohexenyl)ethanol.—Δ^2-Cyclohexenylacetic acid[18] (3.0 g) was treated with 1.6 g of lithium aluminum hydride to give 2.45 g (91%) of a pure colorless liquid: bp 76–77° (2 mm) [lit.[36]

(24) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).
(25) M. N. Das, F. Kern, T. D. Coyle, and W. D. Walters, *ibid.*, **76**, 6271 (1954).
(26) C. L. Wilson, *ibid.*, **69**, 3002 (1947).
(27) D. L. Garin, Ph.D. Thesis, Iowa State University, Ames, Iowa, 1964.
(27a) NOTE ADDED IN PROOF.—The *endo* isomers of the bicyclic carboxaldehydes (**3** and **14**) rearrange to the respective unsaturated acetaldehydes (**2** and **7**) when injected into a gas chromatograph with the injection port heated to 230°.
(28) Melting points and boiling points are uncorrected. Nmr spectra were obtained on a Varian HR-60 spectrometer in CCl_4 with tetramethylsilane as internal standard. Except where otherwise noted, a Perkin-Elmer RX vpc column was used exclusively (a 2-m, 0.25-in. diameter column utilizing Ucon oil LB-550-X on diatomaceous earth). Percentage compositions refer to the relative areas observed for the different components.
(29) O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1220 (1962).
(30) K. M. Korach, R. D. Nielsen, and H. W. Rideout, *ibid.*, **82**, 4328 (1960).
(31) R. Srinivasan, *ibid.*, **84**, 4141 (1962); W. G. Dauben and R. L. Cargill, *J. Org. Chem.*, **27**, 1910 (1962).
(32) FMC Corp., New York, N. Y.
(33) J. Meinwald and R. A. Chapman, *J. Amer. Chem. Soc.*, **90**, 3218 (1968).
(34) R. K. Hill and A. G. Edwards, *Tetrahedron Lett.*, 3239 (1964).
(35) C. R. Noller and R. Adams, *J. Amer. Chem. Soc.*, **48**, 2444 (1926).
(36) L. F. Fieser, M. T. Leffler, *et al.*, *ibid.*, **70**, 3195 (1948).

bp 74–75° (2 mm)]; infrared (CCl_4), 3300, 3030, 3010, 1645, 1448, 1432, 1138, 1067, 1049, 1010, 973, 888, 835, 720, 678, and 662 cm^{-1}.

3,4-Tetramethylene-2,3-dihydrofuran (8).—The major product (56%) from the pyrolysis of **6** displayed the following physical data: infrared (neat), 2910, 2850, 1670, 1470, 1445, 1100, 1085, 1060, 1040, 940, 920, 835, and 788 cm^{-1}; uv max (95% ethanol) 214 mμ (ε 6100).

The enol ether **8** (50 mg) was hydrogenated in ethyl acetate with 5% platinum oxide on charcoal to give essentially one compound as shown by vpc analysis. A sample of the saturated ether collected by preparative vpc showed the following physical data: infrared (CCl_4), 2930, 2860, 2670, 1590, 1480, 1450, 1135, 1082, 1060, 1030, 968, 926, and 892 cm^{-1}; $\delta_{TMS}^{CCl_4}$ (in ppm) 3.6 (m, 4 H, CHO), 2.2 (broad, 2 H, >CH–), and 1.5 (broad single peak, 8 H, CH_2). Both infrared and nmr spectra were superimposable with those of *cis*-hexahydrophthalan (**9**).

***cis*-Hexahydrophthalan (9).**—Following the procedure of Warnell and Shriner for the ozonolysis of an olefin,[19] bicyclo[4.2.0]oct-7-ene[31] (0.50 g, 0.046 mol) in anhydrous ethanol (40 ml) was cooled in an ice bath and a stream of ozone in oxygen (2%) was passed through the solution for 0.5 hr. The ethanol solution was allowed to warm to room temperature and concentrated *in vacuo*. The crude liquid ozonide was dissolved in ether (5 ml) and added dropwise to a stirred suspension of lithium aluminum hydride (1.0 g) in ether (20 ml). The mixture was allowed to stir for 1 hr then refluxed for 0.5 hr. Excess hydride was quenched with water and 2 *N* hydrochloric acid (1 ml) was added. The solution was allowed to stir until hydrolysis was complete. The ether solution was filtered and dried (Na_2SO_4). Removal of the ether *in vacuo* gave 0.50 g of a colorless viscous liquid. A small amount of this liquid was dissolved in ether and induced to crystallize by keeping it in the freezer overnight. The white crystals had mp 40–42° (lit.[37] mp 42–43° for *cis*-hexahydrophthalyl alcohol).

Without further purification, the liquid diol was refluxed with 18% sulfuric acid (2 ml) for 20 min, in a manner similar to that reported[20,21] to give 0.40 g of a liquid with a terpenelike odor which was shown to be essentially one compound by vpc analysis. The infrared spectrum of **9** was identical with that published for *cis*-hexahydrophthalan.[38]

(37) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963).

Bicyclo[3.2.0]heptan-6-one (10).—Following the procedure of Brown and Zweifel for the hydroboration of a olefin,[39] bicyclo[3.2.0]hept-6-ene[29] (18.2 g, 0.19 mol) yielded 17.0 g of a colorless liquid alcohol. Chromic acid oxidation[40] gave 13.0 g of crude product. Distillation afforded 5.0 g (24%) of colorless liquid: bp 65–70° (16 mm) [lit.[41] bp 162–166°]; infrared ($CHCl_3$), 1780 cm^{-1}. The semicarbazone derivative had mp 200–201.5° (lit.[41] mp 198.5–201°).

Bicyclo[4.2.0]octan-7-one (11).—Following the procedure of Brown and Garg for the conversion of olefins into ketones,[24] 3.0 g (0.028 mol) of bicyclo[4.2.0]oct-7-ene[31] gave 1.2 g (35%) of colorless liquid: bp 55–60° (4 mm) [lit.[6] bp 89–90.5° (25 mm)]; infrared (neat), 1780 cm^{-1}.

Pyrolysis of 10.—The pyrolysis of 0.40 g of **10** in the manner described above gave a gas and a low-boiling liquid. The liquid was analyzed by vpc on a Perkin-Elmer RX column[28] at 75°. The retention time of the liquid was identical with that of cyclopentene. A sample of the liquid was collected from the gas chromatograph. The infrared spectrum was superimposable with that of authentic cyclopentene.[42]

Pyrolysis of 11.—The pyrolysis of 0.25 g of **11** in the manner described above gave a gas and a low-boiling liquid. The liquid was analyzed by vpc on a Perkin-Elmer RX column[28] at 75°. The retention time of the liquid was identical with that of cyclohexene. A sample of the liquid, collected from the gas chromatograph, had an infrared spectrum which was superimposable with that of authentic cyclohexene.[42]

Registry No.—**2**, 19656-91-8; **4**, 766-02-9; **4** (α-naphthylurethan derivative), 19656-93-0; **6**, 285-57-4; **7**, 19656-95-2; **7** (2,4-dinitrophenylhydrazone derivative), 19656-96-3; **8**, 19656-97-4; **9**, 13149-01-4; 2-(Δ²-cyclohexenyl)ethanol, 16452-34-9.

Acknowledgment.—The author would like to thank Professor O. L. Chapman for valuable discussions.

(38) J. Entel, C. H. Ruof, and H. C. Howard, *J. Amer. Chem. Soc.*, **74**, 441 (1952).
(39) H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961).
(40) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2952 (1961).
(41) A. T. Blomquist and J. Kwiatek, *ibid.*, **73**, 2098 (1951).
(42) Aldrich Chemical Co., Milwaukee, Wis.

Diels–Alder Adducts of 1,3-Dimethyl-1,3-cyclohexadiene

R. N. MIRRINGTON AND K. J. SCHMALZL

Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia 6009

Received October 22, 1968

The structures and stereochemistry of the major Diels–Alder adducts of 1,3-dimethyl-1,3-cyclohexadiene (**2**) with methyl vinyl ketone, methyl acrylate, and ethyl propiolate have been established as **4a**, **4b**, and **6d**, respectively. Lactonization of acid **4c** afforded either novel δ-lactone **7** or γ-lactone **8** as the major product depending on the conditions used. Lactone **7**, the kinetically stable product, represents the first of such δ-lactones to be isolated in the bicyclo[2.2.2]octane series.

In connection with our work on the total synthesis of novel terpene skeletons, we required a supply of *endo*-1,5-dimethylbicyclo[2.2.2]oct-5-en-2-yl methyl ketone (**4a**). Although a Diels–Alder reaction between 1,3-dimethyl-1,3-cyclohexadiene (**2**) and methyl vinyl ketone would be expected[1] to yield **4a** as the major product, we considered it necessary to make a detailed study of the nature of the adduct(s) from this reaction, particularly since no Diels–Alder adducts of **2** have been described previously, and because the stereochemical and structural integrity of **4a** was vital for our future work.

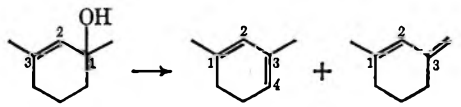
(1) (a) H. L. Holmes, *Org. Reactions*, **4**, 60 (1948); (b) K. Alder, "Newer Methods of Preparative Organic Chemistry," Vol. 1, Interscience Publishers, New York, N. Y., 1948, p 381.

Discussion

1,3-Dimethyl-1,3-cyclohexadiene.—The Grignard addition of methylmagnesium halide to 3-methyl-2-cyclohexen-1-one has been reported several times[2–6] and, except in two cases,[2,6] the product has been described as 1,3-dimethyl-1,3-cyclohexadiene (**2**). However, von Auwers[2] isolated carbinol **1**, which could be dehydrated to a diene, considered by him to be **3**. On the other hand, Thomas and Stoll[6] demonstrated by

(2) K. von Auwers, *Ber.*, **46**, 2988 (1913).
(3) W. N. Haworth, *J. Chem. Soc.*, **103**, 1242 (1913).
(4) A. J. Birch, *ibid.*, 1642 (1947).
(5) (a) R. Y. Levina, N. P. Shusherina, K. D. Gir, and E. G. Treshchova, *Zh. Obshch. Khim.*, **24**, 1551 (1954); *Chem. Abstr.*, **49**, 11571 (1955). (b) R. Y. Levina, V. K. Dauksbas, and T. P. Surikova, *Zh. Obshch. Khim.*, **30**, 2145 (1960); *Chem. Abstr.*, **55**, 8317 (1961).
(6) A. F. Thomas and M. Stoll, *Chem. Ind.* (London), 1491 (1963).

pmr and refractive index studies that the hydrocarbon product of the reaction consisted of **2** and **3** in approximately equal amounts.



1 **2** **3**

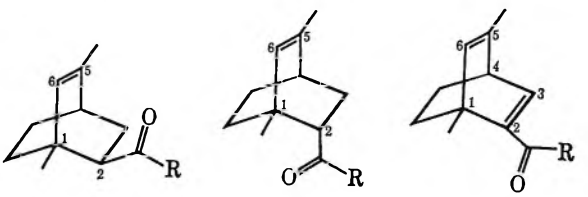
We have found that the decomposition of the Grignard complex is a most critical step in this reaction. When cold aqueous ammonium chloride solution or even ice–water[3] was *added to* the reaction mixture, poor variable yields of dienes were obtained.[7,8] The major product was a high-boiling material whose pmr spectrum showed strong signals at 0.9–1.0 and 5.1 ppm. These signals would be consistent with a substance arising from polymerization of the dienes, but this complex material has not been examined further. However, when the Grignard reaction mixture was decomposed by *adding it to* ice–water,[9] the carbinol **1** was isolated almost quantitatively.

Conditions for acid-catalyzed dehydration of **1** also proved to be critical. Because we initially assumed that the heteroannular diene **3** would take no part in the Diels–Alder reaction under mild conditions,[10,11] we spent some time investigating the possibility of a selective dehydration of **1** to **2**. Mild conditions, such as a solution of **1** in acetic acid or a two-phase system of 5% aqueous sulfuric or perchloric acid shaken with an ethereal solution of **1**, always gave approximately 1:1 mixtures of **2** and **3**. On the other hand, stronger acids, such as a trace of sulfuric or perchloric acid in acetic acid, gave **2**, together with varying quantities of high-boiling material whose pmr spectrum strongly resembled that of the "polymer" observed on decomposition of the Grignard reaction referred to above. The yields of **3** under these conditions were notably diminished, not because of any selective formation of **2**, but because of a more rapid decomposition of **3** to "polymer." Thus, when an approximate equimolar mixture of **1**, **2** and **3** was treated under these strong acid conditions, the product again contained **2** (in reduced amount) and "polymer" with only a trace of **3**.

Further studies on methods of selective formation of **2** (*e.g.*, base-catalyzed E2 elimination of esters derived from **1**) were not pursued when it was found that diene **3** could be forced to participate almost quantitatively in the Diels–Alder reaction under relatively mild conditions.

The Adducts with 1,3-Dimethyl-1,3-cyclohexadiene.—The 1:1 diene mixture was refluxed with methyl vinyl ketone or methyl acrylate containing a trace of hydroquinone in each case. After 3 hr the pmr spectrum of the crude product indicated that all of **2** but virtually none of **3** had reacted. After 14 hr, however, no trace of either diene remained, but a very high yield of adduct (based on the total diene mixture) was obtained—90–95% with methyl vinyl ketone and 75–85% with methyl acrylate. The slow conversion of **3** into adduct under the reaction conditions was shown to be heat dependent, rather than catalyzed by the weakly acidic hydroquinone, when a similar run with methyl vinyl ketone in the absence of hydroquinone also effected 90% conversion into adduct.[12–14]

This product obtained from the prolonged reaction of dienes **2** and **3** with methyl vinyl ketone appeared to be homogeneous by pmr, but vapor phase chromatography (vpc) established the presence of two compounds (**4a** and **5a**) in a ratio of about 8:1. Treatment of this



4 **5** **6**

a, R = Me
b, R = OMe
c, R = OH
d, R = OEt

mixture with sodium methoxide in methanol gave the same two compounds (identical retention times by vpc) but in a ratio of 3:1, respectively. This confirmed the epimeric *endo–exo* relationship of the adducts and also that the major adduct was the more stable.

Similarly, dienes **2** and **3** with refluxing methyl acrylate gave a mixture of adducts **4b** and **5b** in the ratio of 8:1 approximately (pmr and vpc). Alkaline hydrolysis of this mixture gave a solid product from which the major acid **4c** was obtained by fractional crystallization. Addition of methyllithium to a solution of the crude hydrolysis product in ether gave a mixture of ketones **4a** and **5a** in an 8:1 ratio, thus interrelating the two adducts and confirming the analogous modes of reaction of the two dienophiles. An alternative approach to interrelating **4a** with **4c** by a haloform reaction of the former was less rewarding. The crude product did contain up to 60% **4c** (by pmr) but was contaminated by other unidentified acidic materials.

The *endo* configurations of the acetyl and methoxycarbonyl groups in the major adducts (**4a** and **4b**) were suggested by pmr studies initially, and confirmed later by acid-catalyzed lactonization of **4c** (see below). In the pmr spectra (Table I) of the major adducts **4**, the shielding of the R groups by the double bond and of the olefinic proton (H_6) by the carbonyl group indicated[15] the *endo* configuration.

Treatment of **4c** with *hot* aqueous formic acid gave in 73% yield a product whose spectral properties were consistent with **7**. In particular, the C_5-methyl group

(7) Similar problems have been encountered in Grignard reactions with some 2,3-disubstituted 2-cyclohexenones.[8]

(8) J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **88**, 3408 (1966).

(9) von Auwers[2] isolated carbinol **1** by adding the reaction mixture to cold aqueous ammonium chloride solution, but the significance of this reverse addition was apparently not realized by later workers who were unable to isolate **1**.

(10) For example, 3-methylenecyclohexene gives no adduct with maleic anhydride or benzoquinone.[11]

(11) I. N. Nazarov and N. V. Kuznetsov, *Dokl. Akad. Nauk SSSR*, **111**, 358 (1956); *Chem. Abstr.*, **51**, 9504 (1957).

(12) Other heteroannular dienes of type **3**, *e.g.*, β-phellandrene[13] and abietic acid,[14] have also been persuaded to yield adducts with maleic anhydride, but under more forcing conditions and generally in much poorer yields than in the present case.

(13) N. F. Goodway and T. F. West, *J. Chem. Soc.*, 2028 (1938).

(14) L. Ruzicka, P. J. Ankersmit, and B. Frank, *Helv. Chim. Acta*, **16**, 1289 (1932).

(15) A. A. Othman, M. A. Qasseem, and N. A. J. Rogers, *Tetrahedron*, **23**, 87 (1967).

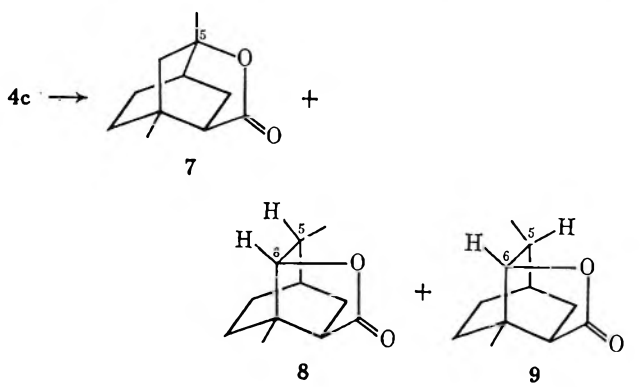
TABLE I
PMR SPECTRA[a] OF ADDUCTS OF 2 AND DERIVATIVES

	H_6[b]	R	C_1-methyl singlet	C_5 methyl[c]
4a	5.51	1.90 s	1.09	1.80
5a	5.51	2.10 s	1.12	1.75
4b	5.45	3.55 s	1.09	1.80
5b	5.56	3.61 s	1.06	1.75
4c	5.48	10.64 br[d]	1.19	1.80
5c	5.57	10.64 br[d]	1.18	1.77
7			1.01	1.37 s
8	4.07 d (6.8)		1.05	1.01 d (7.3)
6c[e]	5.53	12.09 br[d]	1.68	1.74

[a] Determined in CCl_4. Chemical shifts in parts per million downfield from TMS as internal standard with multiplicity and coupling constants (hertz) shown or discussed in footnotes. [b] This proton gave rise to a broad singlet, $W_{1/2}$ = 4.5 Hz except where indicated otherwise. [c] A doublet with J = 2 Hz except where indicated otherwise. [d] Removed after shaking with D_2O. [e] The other olefinic proton (H_3) occurred at 7.33 as a doublet (J = 6.5 Hz) while H_4 appeared as a multiplet at 3.34, clearly separated from other signals.

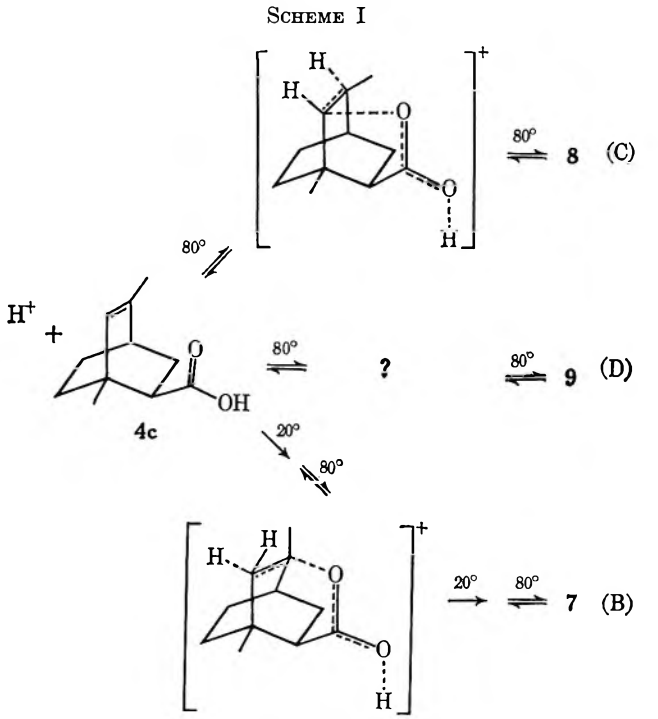
gave rise to a singlet at 1.37 ppm in the pmr spectrum and no signals occurred downfield from 2.5 ppm. Furthermore, the ir maximum in carbon tetrachloride at 1765 cm^{-1} indicated a δ-lactone, in excellent agreement with studies of Wilder and Winston,[16] who report 5.67 ± 0.03 μ (1765 ± 10 cm^{-1}) for a wide variety of δ-lactones; γ-lactones are predicted to absorb near 5.60 μ (1785 cm^{-1}) in the same solvent.[17]

Lactonization of **4c** with hot *anhydrous* formic acid containing concentrated sulfuric acid, in a manner



analogous to that employed with diacid **10**,[18] gave a mixture consisting of four compounds (A, B, C, and D) in the ratio of 0.2:1:3:1 approximately (vpc). A was present in only minor amount and was not identified, while B corresponded to δ-lactone **7**. The major constituent C showed an ir maximum at 1781 cm^{-1} indicating a γ-lactone. Its pmr spectrum contained a doublet at 4.07 ppm whose coupling constant of 6.8 Hz was consistent with the configuration at C_5 represented in **8**, the product expected[19] from a "rearside" or *trans* protonation[20] illustrated in Scheme I. Double irradiation experiments confirmed that H_5 was responsible both for the doublet at 4.07 ppm, assigned to H_6, and for the methyl doublet, when irradiation at 1.95 ppm collapsed each to a singlet in separate experiments. The fourth component D which could not be separated from C appeared to be also a γ-lactone (ir) probably isomeric with the latter. The main difference in the pmr spectrum was the presence of a broad singlet at 3.63 ppm which could be assigned to H_6 in γ-lactone **9** where the dihedral angle between H_6 and H_5 is almost 90°. This assignment of structure **9** to D must nevertheless be regarded as speculative until a purer sample is available.

SCHEME I



A similar mechanism (Scheme I) possibly operates in the formation of **7**, which was shown to be a product of kinetic control by two further experiments. First, treatment of **4c** with *cold* anhydrous formic acid containing concentrated sulfuric acid gave δ-lactone **7** in 80% yield. Second, treatment of **7** with *hot* anhydrous formic acid as described for **4c** gave a mixture of the same four compounds (A, B, C, and D) in similar proportion (by vpc).

The mechanism shown in Scheme I for the formation of **8** from **7** *via* acid **4c** is preferred to the alternative direct conversion of **7** into **8** incorporating a 1,2-hydride shift.

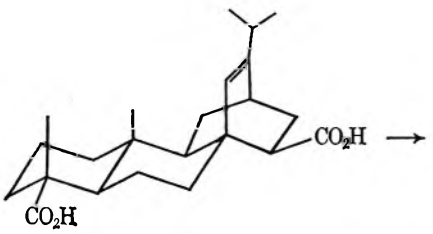
It would be unwise to regard the formation of **8** under such strongly acidic conditions as evidence for the *endo* configuration in the major Diels–Alder adduct, in view of the fact that such conditions could promote epimerization of the *exo* isomer **5c** to **4c** before lactonization, or could possibly convert **5c** into lactonic products by rearrangement.[15] However, the lactone **7** represents more reasonable confirmation of the *endo* configuration in the major adducts (**4**) because of its formation under much milder conditions, which would not be expected to promote skeletal rearrangements. Lactone **7** appears to be the first example of the isolation of such δ-lactones in the bicyclo[2.2.2]octane series. The structure of an

(16) P. Wilder and A. Winston, *J. Amer. Chem. Soc.*, **77**, 5598 (1955).
(17) W. R. Boehme, E. Schipper, W. G. Scharpf, and J. Nichols, *ibid.*, **80**, 5488 (1958).
(18) N. J. Halbrook, R. V. Lawrence, R. L. Dressler, R. C. Blackstone, and W. Herz, *J. Org. Chem.*, **29**, 1017 (1964).
(19) M. F. Ansell and M. H. Palmer, *Quart. Rev.* (London), **18**, 211 (1964).
(20) Similarly, the appearance of a doublet at δ 4.59 (J = 6 Hz) in the pmr spectrum of lactone **11** led to the assignment[18] of the configuration at C_{11} as shown.

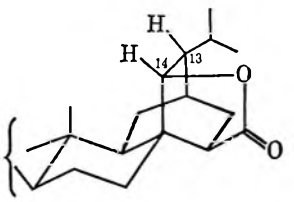
iodo-δ-lactone reported earlier[17] rests on an ir spectrum alone and its isolation could not be repeated.[21]

Our isolation of **7** in good yield prompted us to reexamine the lactonization of the diterpene derivative **10** under milder conditions than were previously used,[18] with a view to obtaining or detecting the corresponding δ-lactone **13**. The requirement of structure **13** that the isopropyl group occupy the hindered side of the molecule appears from models to be of little consequence, because the twisting of the bicyclooctane ring system to form a δ-lactone virtually eliminates any steric crowding of the isopropyl group. Furthermore, this same twisting does not appear from models to affect, or to be affected by, the rigid A and B rings. We were thus reasonably satisfied that **13** would not be in itself too unstable a molecule but did feel that hindrance to protonation at C_{14} by the methyl group at C_{10} could well be significant enough to prevent formation of **13** under the equilibration conditions of lactonization.

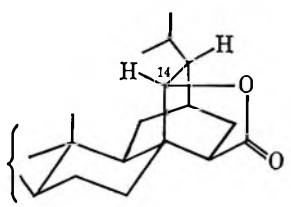
With some reservation then, we treated the diacid **10**[22] with acid under various conditions. Cold formic



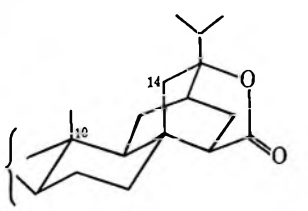
10



11



12



13

acid for 9 hr had no effect while cold formic in the presence of perchloric acid or hot aqueous formic acids gave products whose ir spectra showed the presence of varying amounts of γ-lactone (1780 cm^{-1}) but no absorption due to δ-lactone. One interesting feature emerged from the pmr spectra of the crude lactones. As well as the doublet at 4.59 (H_{14} in **11**), a broad singlet (approximately one-third the intensity of the doublet) appeared at 4.37 ppm and could possibly be assigned to H_{14} in the epimer **12** by analogy with **9** above.

Although the point of attachment (C_2) of the carbonyl-containing group in the adducts **4** and **5** is inferred from the structures of the lactones **7** and **8**, it was verified by examination of the reaction of **2** with propiolic acid and ethyl propiolate, which should react as dienophiles in the same sense as ethyl acrylate.[23] The only product isolated in low yield from the reaction with propiolic acid was 2,4-dimethylbenzoic acid, formed by an Alder–Rickert reaction[24] on the intermediate adduct **6c**. The latter was not isolated in this case, but could be detected in the crude product whose pmr spectrum showed a second olefinic proton as a doublet (J = 6.5 Hz) downfield at 7.33 ppm which was assigned to H_3. The low yield in this reaction was attributed mainly to the significant decomposition of the dienes **2** and **3** under the acidic reaction conditions.

On the other hand, the reaction of the diene mixture with ethyl propiolate proved far more satisfactory. The product consisted of a mixture of adduct **6d** and ethyl 2,4-dimethylbenzoate (4:1) together with unreacted dienes. However, alkaline hydrolysis of this mixture under reflux promoted further Alder–Rickert reaction to give an acidic product consisting of **6c** and 2,4-dimethylbenzoic acid (2:1).

A noteworthy feature of the pmr spectrum of **6c** was the appearance of the C_1 methyl at 1.68 ppm, strongly deshielded by the coplanar carboxylic acid group. This clear demonstration of the vicinal relationship of the two groups, together with the formation of 2,4-dimethylbenzoic acid, firmly established the structure of **6c**. Final proof of structure of the vinyl ketone and acrylate adducts was provided by the reduction of **6c** with lithium–ammonia to a 1:1 mixture of acids, identified as **4c** and **5c** by pmr and by conversion into lactone **7** in excellent yield (based on **4c**).

Experimental Section[25]

1,3-Dimethyl-2-cyclohexen-1-ol (1).—A solution of 110 g of 3-methyl-2-cyclohexen-1-one,[26] bp 82–85° (12 mm), in 110 ml of ether was added dropwise during 1 hr to a stirred solution of methylmagnesium iodide (1.3 equiv) in 1000 ml of ether at 0°. The mixture was refluxed for 4 hr, then poured slowly with stirring into 2.5 l. of water and ice. The organic phase was combined with two 300-ml portions of ether extractions of the aqueous phase, then dried and evaporated to give alcohol **1**: bp 68° (5 mm) [lit.[2] bp 75° (15 mm)]; pmr δ 5.32 (broad s, 1, H_2), 2.95 (s, 1, OH), 1.64 (broad s, 3, vinyl methyl), 1.18 (s, 3, C_1 methyl).

Acid-Catalyzed Dehydration of 1.—A solution of 24 g of **1** in 200 ml of ether was shaken at 0° for 30 min with 200 ml of 5% aqueous perchloric acid; ice was added occasionally to maintain the temperature at 0°. The ether layer was washed thoroughly with water, dried, and evaporated to give a 1:1 mixture of dienes (**2** and **3**). Subsequent reactions on this mixture were performed without delay as slow decomposition was observed on keeping: pmr δ 5.86 (m, H_2 in **3**), 5.48 (q, H_2 in **2**), 5.27 (m, H_4 in **2**), 4.59 (s, C=CH_2 in **3**), 1.77 (m, overlapping C_1 methyls of **2** and **3**), 1.67 (d, C_3 methyl in **2**).

Diels–Alder Reaction of Dienes 2 and 3. A. With Methyl Vinyl Ketone.—A mixture of 15 g of dienes and 30 g of redistilled methyl vinyl ketone containing 0.3 g of hydroquinone was heated

(21) H. W. Whitlock, *J. Amer. Chem. Soc.*, **84**, 3412 (1962).

(22) We are grateful to Professor Werner Herz for a generous sample of this compound.

(23) W. Herz, R. C. Blackstone, and M. G. Nair, *J. Org. Chem.*, **31**, 1800 (1966).

(24) K. Alder and H. F. Rickert, *Ann. Chem.*, **524**, 180 (1936); *Ber.*, **70**, 1354, 1364 (1937).

(25) Melting points are uncorrected. Analyses are by the Australian Microanalytical Service, Melbourne. Infrared spectra were measured on a Perkin-Elmer 337 grating infracord spectrophotometer for carbon tetrachloride solutions unless otherwise stated. Pmr spectra were recorded on a Varian A-60 spectrometer using 8–10% solutions in carbon tetrachloride unless otherwise stated. Double irradiation experiments were carried out using a Varian Model V-6058A spin decoupler. A Perkin-Elmer 880 gas chromatograph was used for vpc analysis with nitrogen carrier gas at a flow rate of 40 ml/min. Columns were 10 ft × 0.125 in. of either 5% Ucon or 5% Hyprose on Chromosorb W (80–100 mesh).

(26) M. W. Cronyn and G. H. Riesser, *J. Amer. Chem. Soc.*, **75**, 1664 (1953).

under reflux for 14 hr. The excess methyl vinyl ketone was removed under reduced pressure to give 26 g of an oil which showed two peaks (8:1) by vpc (5% Ucon, 130°) of retention times 9.7 and 8.3 min assigned to ketones **4a** and **5a**, respectively: ir 1707 cm^{-1} (ketone); pmr signals corresponding to both ketones (see Table I). A similar run in the absence of hydroquinone gave an identical crude product in 90% yield.

Distillation of the crude oil in either case gave only about 75% recovery of a colorless product, bp 75° (0.5 mm), virtually identical with the crude material by vpc and pmr. The decreased yield was accounted for by a high-boiling residue, possibly arising by polymerization of the dienes (from a reverse Diels–Alder) at the relatively high bath temperature of 140° during distillation. As a result, most experiments on **4a** (see below) were carried out on undistilled material.

The ketone **4a** formed a dinitrophenylhydrazone derivative as yellow plates: mp 132.5–133°. *Anal.* Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.72; H, 6.29; N, 15.26.

When 0.5 g of the above ketone mixture (8:1) was refluxed for 1 hr in 15 ml of 4.5 *M* sodium methoxide in methanol, the crude product obtained after usual work-up showed pmr signals again corresponding to **4a** and **5a** but with an increased intensity of the latter. Vpc analysis confirmed the presence of only **4a** and **5a** but in a new ratio of 3:1 which remained constant on similar treatment of the mixture for a further 4 hr.

B. With Methyl Acrylate.—A solution of 11.5 g of the diene mixture and 0.3 g of hydroquinone in 42 g of redistilled methyl acrylate was heated under reflux for 12 hr. The product (17.5 g) obtained by removal of the methyl acrylate under reduced pressure showed two peaks on vpc (5% Hyprose, 110°) with retention times of 2.6 and 2.3 min (8:1) while the pmr spectrum contained signals (Table I) in similar ratio corresponding to **4b** and **5b**, ir 1733 cm^{-1} (ester).

Preparation of Acid 4c.—The mixture of esters **4b** and **5b** (10.5 g) was heated under reflux for 20 hr with 130 ml of 2 *N* aqueous ethanolic sodium hydroxide, then concentrated to remove most alcohols, acidified (10% H_2SO_4) at 0°, and extracted with ether. The acids were extracted from the ethereal phase with 5% sodium carbonate solution and were isolated by acidification (10% H_2SO_4) at 0° and ether extraction. Removal of the ether gave 7.5 g of a solid which afforded *endo* acid **4c** as colorless plates by fractional crystallization from 4:1 water–ethanol: mp 101°; ir (Nujol) 1689 cm^{-1} (acid). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.45; H, 8.72; O, 17.83.

Reaction of Methyllithium with 4c and 5c.—A solution of 0.4 g of **4c** and **5c** (8:1) in 5 ml of dry ether was added slowly with stirring to a solution of methyllithium (from 0.8 g of lithium) in 30 ml of ether at 0°. After 1 hr at 0° and 1 hr at room temperature, the ethereal solution was washed with water and sodium hydroxide solution, dried, and evaporated to give 0.4 g of a mixture of ketones **4a** and **5a**, (8:1), identical by pmr and vpc with the mixture obtained from the Diels–Alder reaction above.

Haloform Reaction on 4a and 5a.—Aqueous sodium hydroxide (3 *N*, 50 ml) and a solution of 15 g of potassium iodide and 7.5 g of iodine in 50 ml of water were each added dropwise simultaneously to a solution of 1.0 g of ketones **4a** and **5a** (8:1) in 100 ml of dioxane with stirring over a period of 1.5 hr; the stirring was continued for a further 2.5 hr. The mixture was concentrated to 50 ml under reduced pressure, diluted with 100 ml of water, and then treated with solid sodium metabisulfite followed by dilute H_2SO_4 at 0°. The precipitated acids were taken up into ether and then extracted with 5% sodium carbonate solution and recovered by acidification (2 *N* H_2SO_4) at 0° and ether extraction to give 0.65 g of product whose pmr spectrum indicated the presence of about 60% **4c**.

Lactonization Experiments on 4c. A. With Aqueous Formic Acid.—An 8:1 mixture of **4c** and **5c** (2.4 g) was added to 70 ml of 80% formic acid and the mixture heated on a steam bath (80°) for 1.5 hr, then cooled, and added slowly to an excess of sodium bicarbonate solution. The crude neutral product (1.5 g, 73% based on **4c**), isolated by exhaustive extraction with ether, crystallized from petroleum ether as colorless square plates of **7**: mp 76–77.5°; ir (CCl_4) 1765 (Nujol), 1750 cm^{-1} (δ-lactone). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.27; H, 8.94; O, 17.79.

B. With Cold Anhydrous Formic Acid.—Purified **4c** (0.12 g) was added to 5 ml of formic acid containing 4 drops of concentrated H_2SO_4 and kept at room temperature for 70 min during which time the mixture became homogeneous. The product was worked up as above to give 0.09 g (75%) of **7**.

C. With Hot Anhydrous Formic Acid.—The foregoing experiment was repeated except that the mixture was heated at 80° for 1.5 hr. Similar work-up gave 0.09 g of a brown oil whose pmr spectrum contained signals corresponding to **7**, **8**, and **9**. Vpc analysis (5% Ucon, 150°) indicated the presence of four components (A, B, C, and D) with retention times of 20.9, 22.6, 24.4, and 26.8 min in a ratio of 0.2:1:3:1, respectively (assuming equimolar response). B and C could be assigned to **7** and **8**, respectively, by direct comparison.

The crude product (0.485 g) from a larger run was chromatographed on 20 g of activity I alumina from which benzene–hexane (1:3) eluted 0.125 g of a mixture of **8** and **9** which showed only two peaks on vpc corresponding to C and D (10:1). The major component **8** crystallized from pentane at −30° as colorless flakes: mp 44–46°; ir 1781 cm^{-1} (γ-lactone). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.33; H, 9.17; O, 17.50.

Benzene–hexane (3:2) eluted 0.27 g of a complex mixture which was not investigated further.

A mixture of 0.15 g of **7** with 5 ml of formic acid and 4 drops of concentrated H_2SO_4 was heated at 80° for 1.5 hr and worked up as above to yield 0.1 g of a brown oil identical (pmr, vpc) with that obtained from **4c**.

Lactonization Experiments on 10. A. With Cold Acid.—A mixture of 0.1 g of **10** and 5 ml of formic acid was kept at room temperature for 9 hr, then diluted with water, and the precipitate collected and dried: ir 1695 cm^{-1} (acid), no lactone absorption.

A similar run with 10 drops of perchloric acid added was monitored by ir of aliquots worked up as described above. Absorption at 1780 cm^{-1} appeared after 1 hr and increased in intensity such that after 8 hr about 10% lactonic material was present: ir 1780 (γ-lactone), 1695 cm^{-1} (acid).

B. With Hot Aqueous Acid.—A suspension of 0.06 g of **10** in 5 ml of 80% aqueous formic acid was heated under reflux for 8 hr. The solvent was removed under reduced pressure below 30° to give a solid consisting of about 10% lactonic material with ir maxima similar to the above: pmr ($CDCl_3$) δ 4.59 (d, J = 6 Hz, H_{14} in **11**), 4.37 (broad s, H_{14} in **12**).

Diels–Alder Reaction of Dienes 2 and 3 with Ethyl Propiolate.—A 1:1 mixture of 8.5 g of the dienes **2** and **3** with 2.05 g of ethyl propiolate[27,28] was heated at 80° until pmr analysis indicated that the latter was consumed (about 10 hr). The acetylenic proton of propiolic ester had disappeared and the characteristic doublet of the ester adduct **6d** at δ 7.12 (H_3) was evident, together with signals corresponding to the dienes and ethyl 2,4-dimethylbenzoate. The mixture was added to a solution of 10 g of sodium hydroxide in 100 ml of ethanol–water (1:1) and refluxed for 4 hr. The solution was acidified with dilute sulfuric acid and extracted with ether from which the acidic material was extracted with aqueous sodium carbonate and thence isolated by acidification and ether extraction as a yellow solid (2.8 g) whose pmr spectrum indicated that it consisted of a 2:1 mixture of 1,5-dimethylbicyclo[2.2.2]octa-2,5-dien-2-oic acid (**6c**) and 2,4-dimethylbenzoic acid. The solid (1.8 g) was chromatographed on a column of 180 g of 20% silver nitrate–silica gel. Elution with benzene–hexane (1:1) afforded 0.43 g of 2,4-dimethylbenzoic acid which crystallized from benzene–hexane: mp 124.5° (lit.[29] mp 126°); identical by mixture melting point, ir, and pmr with an authentic sample prepared by a haloform reaction[29] on 2,4-dimethylacetophenone.

Elution with benzene gave 0.17 g of a mixture of the two acids but benzene–ether (9:1) eluted 0.97 g of **6c** which crystallized from hexane as colorless prisms: melting point indefinite (decomposition[30] together with sublimation occurred between 110 and 130°); ir 1685 cm^{-1} (acid). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.40; H, 7.94.

Lithium–Ammonia Reduction of 6c.—To a suspension of 0.10 g of **6c** in 50 ml of liquid ammonia was added 0.20 g of lithium shot and the blue solution was stirred for 2 hr. After most of

(27) Prepared from acetylene dicarboxylic acid in low yield by the procedure of Perkin and Simonsen.[28]

(28) W. H. Perkin and J. L. Simonsen, *J. Chem. Soc.*, **91**, 816 (1907).

(29) W. H. Perkin and J. F. S. Stone, *ibid.*, 2275 (1925).

(30) The pmr spectrum of a sample heated at 130° for 5 min then diluted with CCl_4 contained signals due to **6c** and 2,4-dimethylbenzoic acid in a ratio of approximately 1:1 together with a sharp singlet at δ 5.33 probably due to a trace of ethylene trapped in the melt.

the ammonia had evaporated, water was added to the residue and the alkaline solution was acidified carefully at 0° with dilute HCl. The precipitate was isolated by ether extraction and evaporation of the dried extracts yielded 0.09 g of a colorless oil consisting of **4c** and **5c** in a ratio of 1:1 estimated by integration of the olefinic signals at 5.48 and δ 5.57.

The foregoing mixture was treated with 5 ml of formic acid containing 4 drops of concentrated H_2SO_4 at 20° for 1 hr. Work-up as described previously for **7** gave 0.04 g of a neutral compound, identified as **7** by pmr and vpc.

Registry No.—**4a**, 19990-29-5; **4a** (2,4-dinitrophenylhydrazone), 19990-30-8; **4b**, 19990-31-9; **4c**, 19990-32-0; **5a**, 19990-33-1; **5b**, 19990-34-2; **5c**, 19990-35-3; **6c**, 19990-36-4; **7**, 19990-37-5; **8**, 19990-38-6.

Bridged Polycyclic Compounds. LVII. The Photorearrangement of 7-Methylenedibenzobicyclo[2.2.2]octadiene. The Preparation and Properties of Dibenzotricyclo[4.2.1.0^{1,3}]octadiene[1]

STANLEY J. CRISTOL AND GWENDOLYN O. MAYO

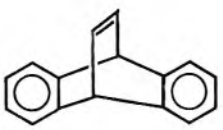
Department of Chemistry, University of Colorado, Boulder, Colorado 80302

Received September 20, 1968

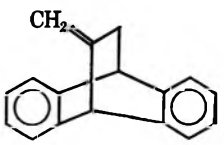
The photorearrangement of 7-methylenedibenzobicyclo[2.2.2]octadiene (**3**) yields dibenzotricyclo[4.2.1.0^{1,3}]-nonadiene (**4**) whose structure was determined by spectroscopic and chemical means. Upon hydrogenation cyclopropane **4** gives 5-methyldibenzobicyclo[3.2.1]octadiene (**12**). Treatment of **4** with perchloric acid in acetic acid gives dibenzobicyclo[4 2.1]nona-2,7-dien-6-ol acetate (**15**).

Our interest[1,2] in the chemistry of dibenzotricyclo-[3.3.0.0^{2,8}]octadiene (**1**) and its analogs naturally led us to the use of Ciganek's procedure[3] for the synthesis of **1** and its analogs by sensitized photorearrangements of dibenzobicyclo[2.2.2]octatriene (**2**) and its analogs. When 7-methylenedibenzobicyclo[2.2.2]octadiene (**3**) became available in our laboratory, we were attracted to a study of its photochemical behavior.

1

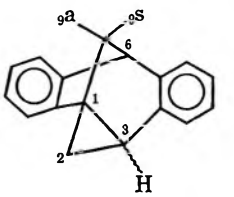


2

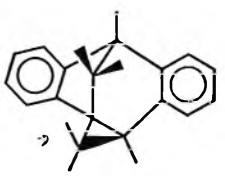


3

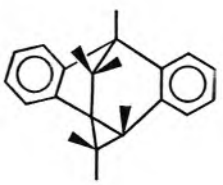
Irradiation of **3** in acetone gave a single compound whose pmr spectrum was initially difficult to interpret. However, at this time, a communication by Zimmerman and his coworkers appeared,[4] which suggested a general mechanism for the isomerization of divinylmethanes to vinylcyclopropanes. If a mechanism similar to that proposed by Zimmerman obtained in the phototransformation of **3**, one (or both) of the geometric isomers of the spirocyclopropane **4**, dibenzotricyclo[4.2.1.0^{1,3}]-nonadiene, would result. In one of the isomers (*exo* **4a**), the cyclopropane ring is *syn* to the methano bridge and, in the other (*endo* **4b**), *anti* to it. The pmr spectrum of the photoproduct is consistent with either **4a** or **4b**. The preparation of **3** by base-promoted dehydrohalo-



4

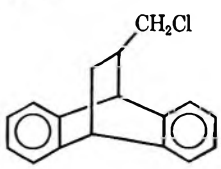


4a

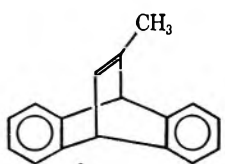


4b

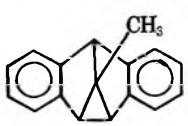
genation of 7-chloromethyldibenzobicyclo[2.2.2]octadiene (**5**) with potassium *t*-butoxide in dimethyl sulfoxide produced a hydrocarbon mixture that consisted largely (*ca.* 90%) of olefin **3**, contaminated with 7-methyldibenzobicyclo[2.2.2]octatriene (**6**).[5] When this mixture of olefins **3** and **6** was used for the photorearrangement reaction in acetone solution, two other cyclopropanes (compounds **7** and **8**)[6] were produced in addition to **4**.



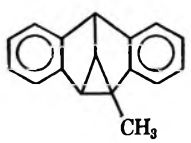
5



6



7



8

(1) Previous paper in series: S. J. Cristol, R. J. Bopp, and A. E. Johnson, *J. Org. Chem.*, in press.

(2) See, for example, (a) S. J. Cristol and B. B. Jarvis, *J. Amer. Chem. Soc.*, **88**, 3095 (1966); **89**, 5885 (1967). (b) S. J. Cristol and B. B. Jarvis, *ibid.*, **89**, 401 (1967). (c) unpublished work of S. J. Cristol, W. Y. Lim, and A. R. Dahl.

(3) E. Ciganek, *J. Amer. Chem. Soc.*, **88**, 2882 (1966).

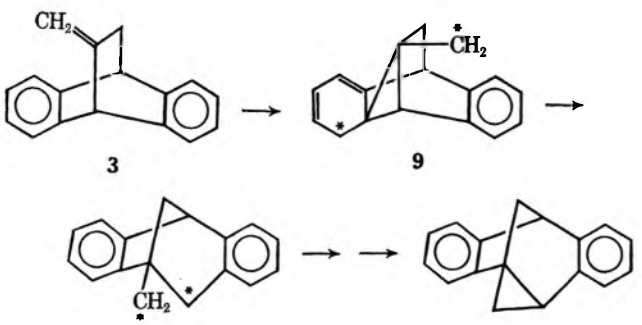
(4) H. E. Zimmerman, R. W. Binkley, R. S. Givens, and M. S. Sherwin, *ibid.*, **89**, 3933 (1967).

(5) The powerful base utilized in the dehydrohalogenation caused prototropic equilibration of **3** and **6**.

(6) The photochemical behavior of olefin **6** and other substituted ethenoanthracenes is currently under study in these laboratories. The resuts of these studies, as well as proofs of structure of compounds **6**, **7**, and **8**, will appear in a later paper.

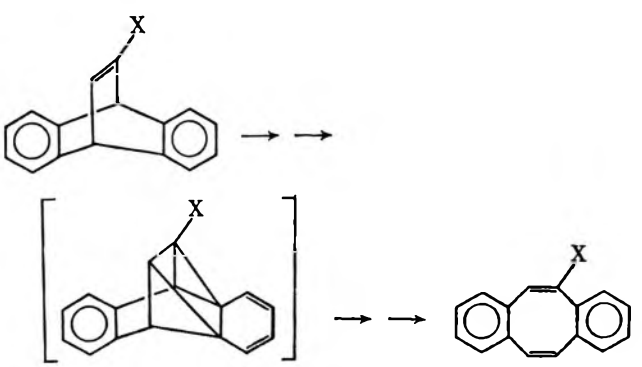
We were unable to prepare a pure sample of olefin **3** by fractional crystallization of the dehydrohalogenation mixture. Pure **3** was, however, readily obtained by utilizing the greater photoreactivity of **6**. When the mixture of **3** and **6** was irradiated for 4 days in acetone, a pmr spectrum showed that the yield of **4** was about 25%, and that **6** had completely reacted to give **7** and **8**. The cyclopropanes **4**, **7**, and **8** were separated from olefin **3** by chromatography on a silver nitrate impregnated column of alumina. Olefin **3** was now easily purified by crystallization and a pure sample upon irradiation gave only cyclopropane **4**.

As indicated above, the Zimmerman mechanism[4] for the photosensitized rearrangement of divinylmethanes predicts the formation of **4** from **3**.



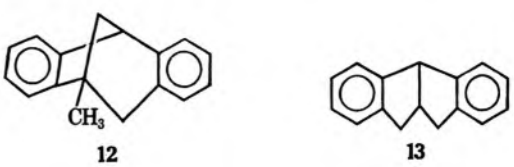
3 **9** **10** **4**

Under singlet conditions (cyclohexane solution) dibenzobicyclo[2.2.2]octatrienes undergo rearrangement to give dibenzocyclooctatetraenes[7] *via* di(arylvinyl)-bridged intermediates or transition states **11**,[8] rather than tricyclic compounds related to **1**, which are produced in the presence of triplet sensitizers. However, **3** was observed to give **4** not only in acetone or benzene solution, but also in cyclohexane. It seems possible that, as no ready path for isomerization analogous to **11** exists for **3**, its singlet lifetime is great enough to allow it to suffer intersystem crossing to its T_1 state, with consequent reaction *via* the Zimmerman mechanism. An interesting observation, which we are presently following up, is that irradiation of mixtures of **3** and **6** leads to methylcyclooctatetraene (from **6**) but to no photoproduct from **3**, at least initially.[9]



11

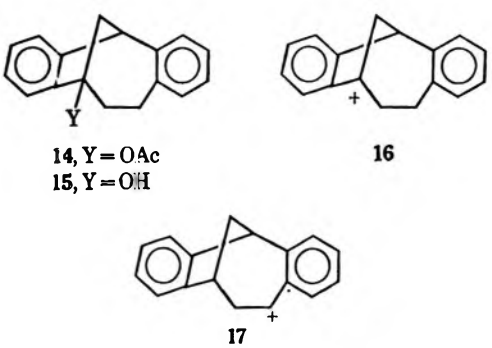
In beginning a study of the chemistry of **4**, we have studied its catalytic hydrogenation and addition of acetic acid. Hydrogenation of **4** over palladium on charcoal leads to a compound whose pmr spectrum (three-proton singlet) indicates a bridgehead methyl group and is otherwise consistent with structure **12**, 5-methyldibenzobicyclo[3.2.1]octadiene. It is of interest that hydrogenation of **1** leads to dibenzobicyclo[3.3.0]octa-2,7-diene (**13**);[2b,3] that is, rupture occurs between the benzylic carbon atoms. However, this is not the case with **4**, which follows the normal hydrogenolysis mode in cyclopropanes, where the bond most likely to be cleaved is that joining the two least substituted carbon atoms.[10] Also, models of both **4a** and **4b** suggest that steric factors would hinder the approach of the benzylic sites to the catalyst surface. The mode of cleavage unfortunately gives no insight into the **4a**–**4b** structural question.



12 **13**

Treatment of **4** with perchloric acid in acetic acid gave dibenzobicyclo[4.2.1]nona-2,7-dien-6-ol acetate (**14**) which was converted by saponification into the corresponding alcohol **15**. Alcohol **15** could not be acetylated either by acetic anhydride in benzene–pyridine or by perchloric acid in acetic acid (the same conditions used for the ring-opening reaction). This evidence indicates that **15** is a tertiary alcohol.

It would appear that electrophilic proton attack on **4** occurs in such a fashion as to give the tertiary benzylic cation **16** rather than the secondary benzylic cation **17** (or [3.2.1] cations), in spite of the fact that **16** is a bridgehead cation. Ion **16** does lie outside the limitations of Bredt's rule for bridgehead transient intermediates, as modified by Fawcett[11] (the sum of the number of atoms in the bridges should be seven or more) or by Wiseman[12] (the largest ring must contain seven or more members).



14, Y = OAc
15, Y = OH
16
17

(7) P. W. Rabideau, J. B. Hamilton, and L. Friedman, *J. Amer. Chem. Soc.*, **90**, 4465 (1968).

(8) H. E. Zimmerman, R. S. Givens, and R. M. Pagni, *ibid.*, **90**, 4191, 6096 (1968).

(9) S. J. Cristol and G. O. Mayo, work in progress.

(10) R. L. Augustine, "Catalytic Hydrogenation," M. Dekker, Inc., New York, N. Y., 1965, pp 133–134, and references therein.

(11) F. S. Fawcett, *Chem. Rev.*, **47**, 219 (1950).

(12) J. R. Wiseman, *J. Amer. Chem. Soc.*, **89**, 5966 (1967).

Experimental Section[13]

7-Methylenedibenzobicyclo[2.2.2]octadiene (3).—To a solution of 7-chloromethyldibenzobicyclo[2.2.2]octadiene (**5**)[15] (5.00 g, 19.6 mmol) in 100 ml of dry dimethyl sulfoxide (decanted from molecular seives) was added potassium *t*-butoxide (4.0 g, 35 mmol). After 1 day, the solution was poured into ice-cold water. Extraction with ether followed, and the organic layer was washed with four portions of water and dried ($MgSO_4$). The solvent was removed by rotary evaporation and the residue was crystallized from 95% ethanol (charcoal). The product (3.91 g, 92% yield) had mp 102–104°. Pmr analysis indicated that the product contained about 90% olefin **3**[16] and about 10% 7-methyldibenzobicyclo[2.2.2]octatriene (**6**).

Photorearrangement of Olefin 3. A. In Acetone.—The olefin mixture (3.06 g, 14.0 mmol), prepared by dehydrohalogenation of the chloromethyl compound **5**, was dissolved in enough reagent grade acetone to completely fill a long-necked round-bottom quartz flask (about 500 ml). Nitrogen was bubbled through the solution for 20 min. The solution was irradiated for 1 week. The acetone was removed by rotary evaporation and the orange residue was chromatographed on Merck 71707 alumina in order to remove the colored material. A hydrocarbon mixture (812 mg) was eluted by petroleum ether (bp 60–70°). The mixture consisted of 17% olefin **3**, 70% cyclopropane **4** (19% yield), 4% cyclopropane **8**, and 9% cyclopropane **7** (pmr analysis). The cyclopropanes were separated from the olefin by chromatography on a 10% silver nitrate impregnated column of Merck 71707 alumina.[17] Good separation resulted when the weight ratio of support to olefin was about 30:1. The oily cyclopropanes were eluted by olefin-free petroleum ether (bp 60–70°) and hydrocarbon **3** was recovered by elution with benzene.

Olefin **3** (recovered in this way from several photoreactions) was purified by recrystallization from 95% ethanol to mp 104.5–106.0°; uv max (C_2H_5OH) 272 mμ (ε 1985), 265 (1630), and 259 (1080). This material (2.012 g, free of olefin **6** and the cyclopropanes) was irradiated for 5 days in 120 ml of reagent grade acetone. A pmr spectrum of the colorless oil (1.255 g, 62.4%) eluted during the chromatography on Merck 71707 alumina indicated the presence of olefin **3** (59.2%) and cyclopropane **4** (40.8%) only. The yield of **4** was therefore 512 mg (25.4% of theoretical) or 40.3% based on unrecovered starting material.

An analytical sample of cyclopropane **4**, mp 50.0–51.5°, was prepared by another chromatography on silver nitrate–alumina and a short-path distillation (80°, 0.6 mm): uv max (C_2H_5OH) 276 mμ (ε 1870), 269 (1950), and 258 (1340); pmr[18] H_{9s} (τ 8.97, doublet, J = 10 Hz, dihedral angle $H_6C_6C_9H_{9s} \simeq 90°$, shielded by cyclopropane ring[19]), H_{9a} (τ 7.04, doublet of doublets, J = 4, 10 Hz, geminal coupling and vicinal coupling with H_6, somewhat deshielded by cyclopropane ring), H_6 (τ 6.37, doublet, J = 4 Hz), H_3 (τ 7.80, doublet of doublets, J = 6, 8 Hz, cyclopropano and benzylic), and 2 H_2 (τ 8.23, doublet of doublets, J = 6, 7 Hz) (τ 9.23, doublet of doublets, J = 7, 8 Hz).

Anal. Calcd for $C_{17}H_{14}$: C, 93.53; H, 6.47. Found: C, 93.44; H, 6.51.

In other runs, it was found that a 4-day reaction time gave similar results. Also, the deaeration had no apparent effect on the yield.

B. In Benzene.—The mixture of olefins **3** and **6** (487 mg, *ca.* 90% **3** and 10% **6**) was irradiated at 2537 Å in 100 ml of thiophene-free benzene in a quartz tube for 5 days. Olefin **3** was converted into **4** in 21% yield, while the endocyclic olefin **6** was totally transformed to 2-methylcyclooctatetraene (pmr analysis).[9]

C. In Cyclohexane.—A solution of pure olefin **3** (397 mg, free of olefin **6**) in 35 ml of spectral grade cyclohexane was placed in a quartz tube. Prepurified nitrogen was bubbled through the solution for 20 min and then the solution was irradiated (2537 Å) under nitrogen for 3 days. At this time pmr analysis showed the presence of 43% cyclopropane **4** and 57% unreacted **3**.

Hydrogenation of Dibenzotricyclo[4.2.1.0^{1,3}]nonadiene (4).—Cyclopropane **4** (475 mg, 218 mmol) was hydrogenated in the presence of 10% palladium on charcoal (494 mg) in 50 ml of 95% ethanol at atmospheric pressure in the Brown[2] apparatus.[20] The reaction required about 4 hr. The catalyst was removed by filtration and the solvent was removed by rotary evaporation. The pmr spectrum indicated that no starting material remained and that the major product (>80%) was 5-methyldibenzobicyclo[3.2.1]octadiene (**12**). The colorless oil was crystallized from 95% ethanol, mp 47.5–50.0°. An analytical sample of **18** was sublimed (60°, 1.5 mm): pmr[15] 3 H (τ 8.55, singlet), H_1 (τ 6.13, doublet, J = 4 Hz), H_{4x} (τ 7.00, doublet, J = 17 Hz), H_{4n} (τ 7.42, doublet of doublets, J = 17, 1 Hz, geminal coupling and "W"[21] coupling with H_{8a}), H_{8a} (τ 7.73, multiplet, J = 4, 10, 1 Hz), and H_{8s} (τ 8.04, doublet, J = 10 Hz, geminal coupling).

Anal. Calcd for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.80; H, 7.43.

Addition of Acetic Acid to Dibenzotricyclo[4.2.1.0^{1,3}]nonadiene (4).—Cyclopropane **4** (278 mg, 1.275 mmol) was dissolved in 16 ml of 0.1 *M* perchloric acid in acetic acid. The solution was allowed to stand at room temperature for 21 hr. The reaction was quenched by addition of water. The slurry was extracted by chloroform and the combined extracts were washed with water and aqueous sodium bicarbonate and dried ($MgSO_4$). The solvent was removed by rotary evaporation. A pmr spectrum of the oily residue showed only one acetate methyl singlet (τ 7.98), H_1 (τ 5.74, doublet, J = 7 Hz), and 6 $H_{4,5,9}$ (τ 7–9, unresolved multiplets). Spin decoupling showed only that H_1 couples with a proton, presumably H_{9a}, which absorbs at τ 7.3. Acetate **14** (dibenzobicyclo[4.2.1]nona-2,7-dien-6-ol acetate) was not purified but was saponified by potassium hydroxide (1.5 ml of a 1 *M* solution) in refluxing ethanol (20 ml) overnight. Most of the ethanol was removed by rotary evaporation. The residue was extracted by chloroform. The organic layer was washed with water until neutral and then dried ($MgSO_4$), filtered, treated with decolorizing charcoal, and filtered again. The chloroform was removed and dibenzobicyclo[4.2.1]nona-2,7-dien-6-ol (**15**) was crystallized from ethanol (charcoal) as needles: mp 161–163° (three more crystallizations raised this to 163–163.5°) (220 mg, 73% yield over-all): pmr H_1 (τ 5.89, doublet, J = 7.5 Hz), 7 $H_{4,5,9,OH}$ (τ 7 to 9, unresolved multiplet, expansion on HA-100 showed no singlet or doublet 3 H absorptions; H_1 couples with a proton, H_{9a}, which absorbs at τ 7.4).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.83. Found: C, 86.40; H, 6.89.

Attempted Acetylation of Dibenzobicyclo[4.2.1]nona-2,7-dien-6-ol (15).—Alcohol **15** (214 mg, 0.907 mmol), acetic anhydride (2.0 ml, 21 mmol), and 10 ml each of dry pyridine and benzene were combined and allowed to stand at room temperature for 2 days. The mixture was poured onto a slurry of ice and concentrated hydrochloric acid. After 1 hr the mixture was transferred to a separatory funnel with the aid of more benzene and the organic layer was washed with 10% hydrochloric acid and then sodium bicarbonate solution and finally dried ($MgSO_4$). The solvent was removed by rotary evaporation and the colorless solid residue was subjected to pmr analysis. Only absorptions due to starting material were observed in the spectrum.

The recovered alcohol **15** was then dissolved in 25 ml of a 0.1 *M* solution of perchloric acid in acetic acid. The solution was allowed to stand at room temperature overnight. Pmr analysis of the colorless solid, mp 158–160°, recovered from the reaction mixture indicated that only alcohol **15** was present.

Registry No.—**3**, 19978-14-4; **4**, 19978-15-5; **12**, 19978-16-6; **15**, 19978-17-7.

Acknowledgments.—This work was supported by the National Science Foundation. The authors wish to thank Professor A. D. Norman and Professor R. A. Newmark for help in interpretation of the pmr spectra.

(13) Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. The irradiations were carried out in an air-cooled Rayonet[14] photoreactor using lamps emitting radiation mainly at 2537 Å. Ultraviolet spectra were obtained on a Cary 14 recording spectrometer. Proton magnetic resonance spectra were obtained on Varian A-60, A-60A, and HA-100 spectrometers. All chemical shifts are in τ units. Tetramethylsilane was used as an internal standard. The coupling constants given are observed values. Spin–decoupling experiments were conducted on the A-60A and HA-100 instruments.

(14) Southern New England Ultraviolet Co., Middletown, Conn.

(15) K. Alder and E. Windemuth, *Ber.*, **71**, 1939 (1938).

(16) V. J. Shiner and J. S. Humphrey, *J. Amer. Chem. Soc.*, **85**, 2416 (1963).

(17) L. R. Chapman and D. F. Kuemmel, *Anal. Chem.*, **37**, 1598 (1965).

(18) Compare with spectrum of dibenzobicyclo[3.2.1]octadiene in S. J. Cristol, J. R. Mohrig, and D. E. Plorde, *J. Org. Chem.*, **30**, 1956 (1965).

(19) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3218 (1963), and references therein.

(20) Delmar Laboratories, Maywood, Ill.

(21) A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Lett.*, 233 (1964).

Preparation and Reactions of Some [2.2]Paracyclophane Derivatives[1]

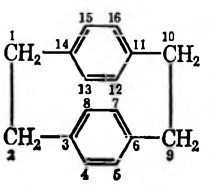
YING L. YEH AND WILLIAM F. GORHAM

Union Carbide Corporation, Technical Center, Bound Brook, New Jersey 08805

Received May 29, 1968

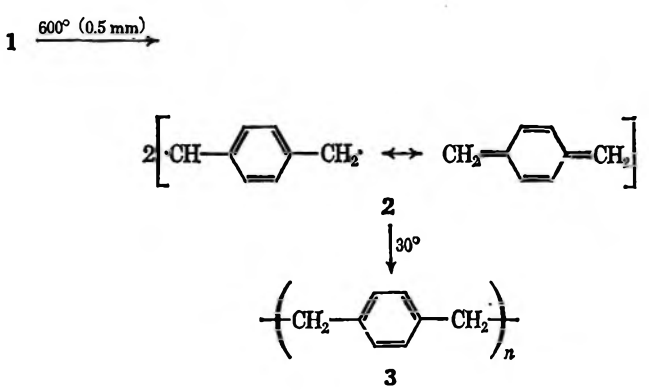
[2.2]Paracyclophane undergoes both normal and abnormal substitution reactions. Direct alkylation of [2.2]paracyclophane at low temperatures results in exclusive monoalkylation instead of the expected polyalkylation. Halogenation of [2.2]paracyclophane gives rise to normal halogenated products with good selectivity. Mono- and dibromo[2.2]paracyclophanes form the corresponding mono- and dilithio[2.2] paracyclophanes upon treatment with butyllithium at elevated temperatures. Treatment of the lithio derivatives with numerous electrophiles results in the formation of substituted paracyclophanes in high yields. Cyanation of 4,16-dibromo[2.2]-paracyclophane produces two isomers of dicyano[2.2]paracyclophanes, namely, 4,16- and 8,16-dicyano[2.2]-paracyclophanes.

[2.2]Paracyclophane (**1**) is the smallest member of the paracyclophanes known to exist. It exists in a definite geometry with hindered rotation of the benzene rings, and possesses severely deformed and strained bond angles and bond lengths.[2,3] As the result of the strain



1

existing in the molecule, [2.2]paracyclophane can be quantitatively pyrolyzed at 600° and less than 1-mm pressure to form two molecules of *p*-xylylene (**2**). These reactive intermediates polymerize on condensation to form poly(*p*-xylylene) (**3**) as shown.[4]



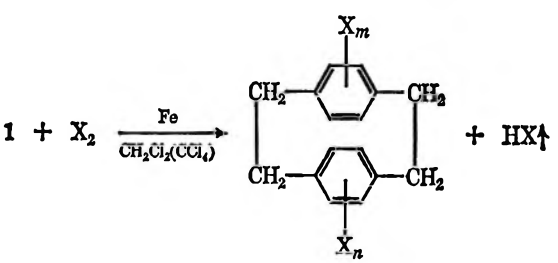
2 **3**

In spite of the numerous monosubstituted derivatives of [2.2]paracyclophane known to date,[3,5-9] di- and polysubstituted [2.2]paracyclophanes, which possess one or more substituents on each benzene ring, were not readily available prior to this work. Cram and coworkers reported the preparation of dinitro-[2.2]paracyclophanes,[10] but the yields were poor and the reaction conditions ill-defined.[11] Cram and coworkers have shown that the main difficulty in effecting di- or polysubstitution on both benzene rings is due to the transannular interaction of the two benzene rings functioning as one single nucleophile.[5-8,10,12,13]

As part of our effort to prepare various di- and polysubstituted [2.2]paracyclophanes as novel precursors to different poly(*p*-xylylenes), and also to understand the chemistry of [2.2]paracyclophane in more detail, an investigation of methods for the preparation of di- and polysubstituted [2.2]paracyclophanes was undertaken.

Results and Discussion

Halogenation of [2.2]Paracyclophane.—[2.2]Paracyclophane undergoes bromination and chlorination reactions readily at room temperature in the presence of a catalytic amount of iron powder or other Lewis acids to give brominated and chlorinated [2.2]paracyclophanes **4** in quantitative yield.[14] The products are cleanly ring-brominated and ring-chlorinated [2.2]paracyclophanes containing up to two bromines or three chlorines on each ring. The amount of side-chain halogenation is minimal (<1%). The halogenation reactions are very selective with respect to the number of halogens introduced on each ring. For example, it is possible to obtain dihalogenated [2.2]paracyclophanes ($m = 1$, $n = 1$) with one halogen on each benzene ring in nearly 95% purity as isolated. The impurities consist mainly of lower and/or higher halogenated homologs. Repeated crystallization of the dichlorinated product yields a pure isomer, 4,16-dichloro[2.2]paracyclophane (**5**), mp 212–213°, while the dibrominated



4, X = Br(Cl)
m = 1–2 (3)
n = 0–2 (3)

(1) Presented at the Macromolecular Chemistry (IUPAC) Meeting, Tokyo, Japan, Sept 1966.

(2) C. J. Brown and A. J. Farthing, *Nature*, **164**, 915 (1949); D. J. Cram, *J. Amer. Chem. Soc.*, **73**, 5691 (1951); C. J. Brown, *J. Chem. Soc.*, 3265 (1953).

(3) K. C. Dewhirst and D. J. Cram, *J. Amer. Chem. Soc.*, **80**, 3115 (1958).

(4) W. F. Gorham, *J. Polym. Sci.*, **4**, 3027 (1966); W. F. Gorham (Union Carbide Corp.), U. S. Patent 3,342,754 (1967); U. S. Patent 3,288,728 (1966).

(5) D. J. Cram and N. L. Allinger, *J. Amer. Chem. Soc.*, **77**, 6289 (1955).

(6) D. J. Cram and L. A. Singer, *ibid.*, **85**, 1075 (1963); L. A. Singer and D. J. Cram, *ibid.*, **85**, 1080 (1963).

(7) D. J. Cram, *Rec. Chem. Progr.*, **20** (2), 71 (1959).

(8) D. J. Cram and R. H. Bauer, *J. Amer. Chem. Soc.*, **81**, 5971 (1959).

(9) D. F. Pollart (Union Carbide Corp.), U. S. Patent 3,164,625 (1966).

(10) D. J. Cram, *et al.*, *J. Amer. Chem. Soc.*, **81**, 5977 (1959).

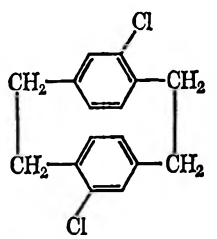
(11) D. J. Cram, private communication.

(12) D. J. Cram and D. J. Wilkinson, *J. Amer. Chem. Soc.*, **82**, 5721 (1960).

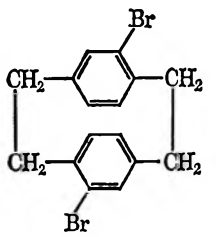
(13) D. J. Cram, *et al.*, *ibid.*, **80**, 3126 (1958).

(14) W. F. Gorham (Union Carbide Corp.), U. S. Patent 3,221,068 (1965).

product yields a pure isomer, 4,16-dibromo[2.2]paracyclophane (**6**), mp 245–246°. Both possess a point of



5

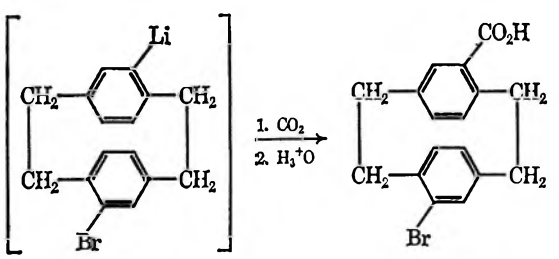


6

symmetry within the molecule. The structure for **6** was elucidated by Reich and Cram[15] using nmr. Our own studies of **5** and **6** using mass spectroscopy, gas phase chromatography, and polymerization experiments[4] confirm that each benzene ring contains one halogen. The dipole moment data are not conclusive owing to the very limited solubility of **5** and **6** in common solvents.

Halogen–Lithium Exchange Reaction.—Halogen-lithium exchange between brominated [2.2]paracyclophane and *n*-butyllithium proceeds in the presence of a catalytic amount of copper powder to form lithio[2.2]-paracyclophanes, a useful reactive intermediate which leads to various substituted [2.2]paracyclophane derivatives.[16–18] For example, treatment of 4,16-dibromo-[2.2]paracyclophane (**6**) with *n*-butyllithium in refluxing benzene gives, in quantitative yield, 4,16-dilithio[2.2]-paracyclophane (**7**) which reacts, *in situ*, with various reagents to form substituted [2.2]paracyclophanes **8**, **9**, **10** (Scheme I). These are just a few examples of the numerous transformations possible from the versatile lithio intermediate. The transformations to the final products from **6** proceed without any isomerization as evidenced by the quantitative recovery of **6** from **7** upon addition of bromine to **7**.

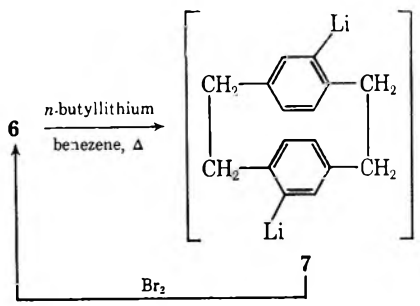
If, however, boiling diethyl ether was used instead of boiling benzene in the exchange reaction of **6** with *n*-butyllithium, only one bromine is replaced by lithium and monolithiomonobromo[2.2]paracyclophane **12** results.

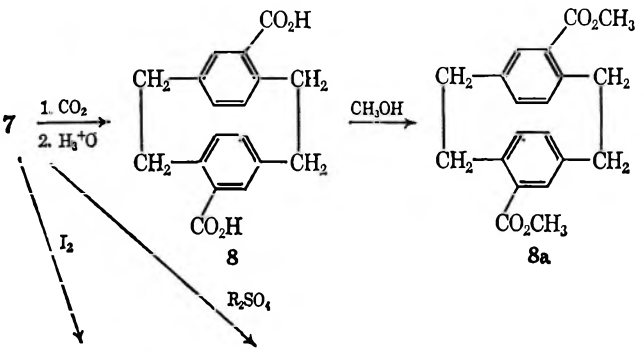


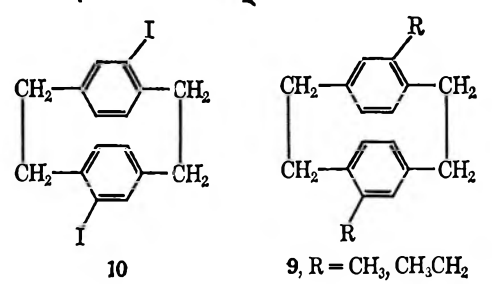
12 **13**

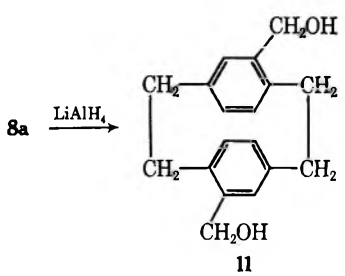
Cyanation Reactions of Brominated[2.2]Paracyclophanes.—Cyanation of 4,16-dibromo[2.2]paracyclophane (**6**) with cuprous cyanide[19] proceeds smoothly at the temperature range of 230–240° with or without a solvent, although use of a solvent is preferred. A proper reaction temperature is the key to the success of

Scheme I





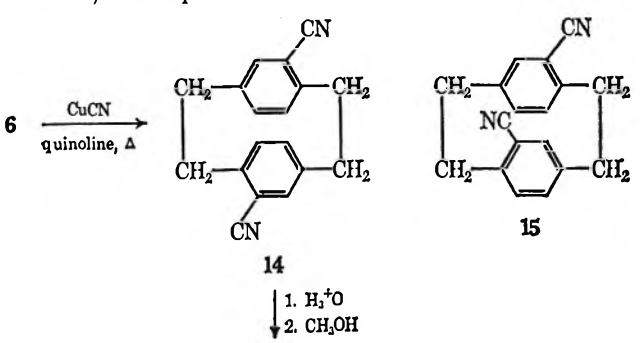




10 **9**, R = CH_3, CH_3CH_2

11

this reaction. This can be shown from the fact that at a temperature lower than 200° or at normal cyanation conditions, *e.g.*, 150° in dimethylformamide, the cyanation reaction of **6** fails to take place. Cyanation of **6** leads to approximately equal amounts (by gas phase chromatography) of two distinct isomers of dicyanated [2.2]paracyclophanes. One of the isomers was shown to be **14**, which possesses the same isomeric structure as



14 **15**

8a

(15) H. J. Reich and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 1365 (1968).

(16) Y. L. Yeh (Union Carbide Corp.), U. S. Patent 3,349,142 (1967). For halogen–lithium interchange reactions involving normal aromatic systems, see H. Gilman and J. Morton, *Org. Reactions*, **8**, Chapter 6 (1954).

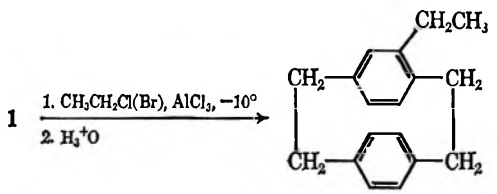
(17) Y. L. Yeh (Union Carbide Corp.), Canadian Patent 705,457 (1965).

(18) Y. L. Yeh (Union Carbide Corp.), Canadian Patent 772,189 (1967).

(19) Y. L. Yeh (Union Carbide Corp.), U. S. Patent 3,155,712 (1964).

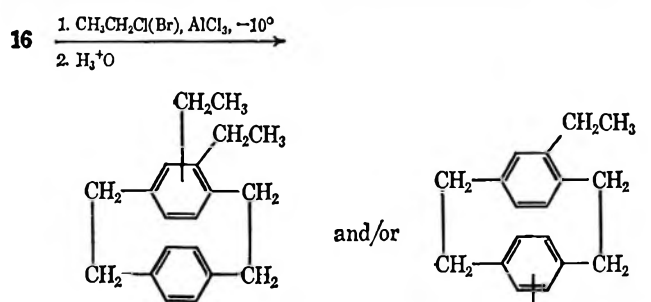
6, by its conversion to the same dicarbomethoxy derivative **8a**. Subsequent elegant studies made by Cram and coworkers on this reaction and other related reactions culminated in the finding[20] that the other isomer is **15**, formed by a mechanism of "ring opening" in which either **6** or **14** splits open at one of the cyclophane bridges followed by rotation of one of the benzene rings and subsequent closure of the bridge.

Alkylation Reactions of [2.2]Paracyclophane.—Treatment of [2.2]paracyclophane with alkyl halides in the presence of aluminum chloride at a temperature lower than $-10°$ results in the formation of monoalkyl[2.2]-paracyclophane upon hydrolysis.[21] For example, monoethyl[2.2]paracyclophane (**16**) is obtained exclusively when [2.2]paracyclophane is treated with ethyl chloride (or bromide) and aluminum chloride in tetrachloroethane at $-10°$. Even with a large excess



16

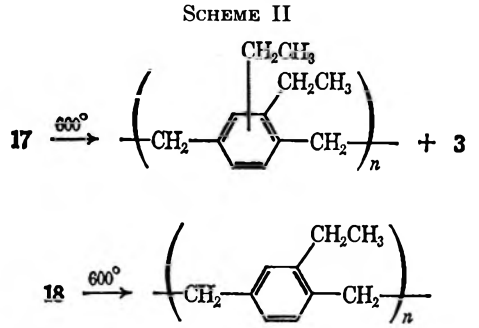
of alkyl halides and aluminum chloride, only monoalkylated products result. Monoalkylated [2.2]paracyclophanes can be alkylated further to give dialkylated [2.2]paracyclophanes. The structures of the dialkylated [2.2]paracyclophanes have not yet been



17 18

elucidated. However, based on a finding that no detectable amount of the unsubstituted poly(*p*-xylylene) (**3**) was isolated upon polymerization of the diethylated [2.2]paracyclophane, it is probable that the diethylated product consists mainly of **18** and not the expected **17** (see Scheme II); this is possible only through close transannular interaction between the two benzene rings.

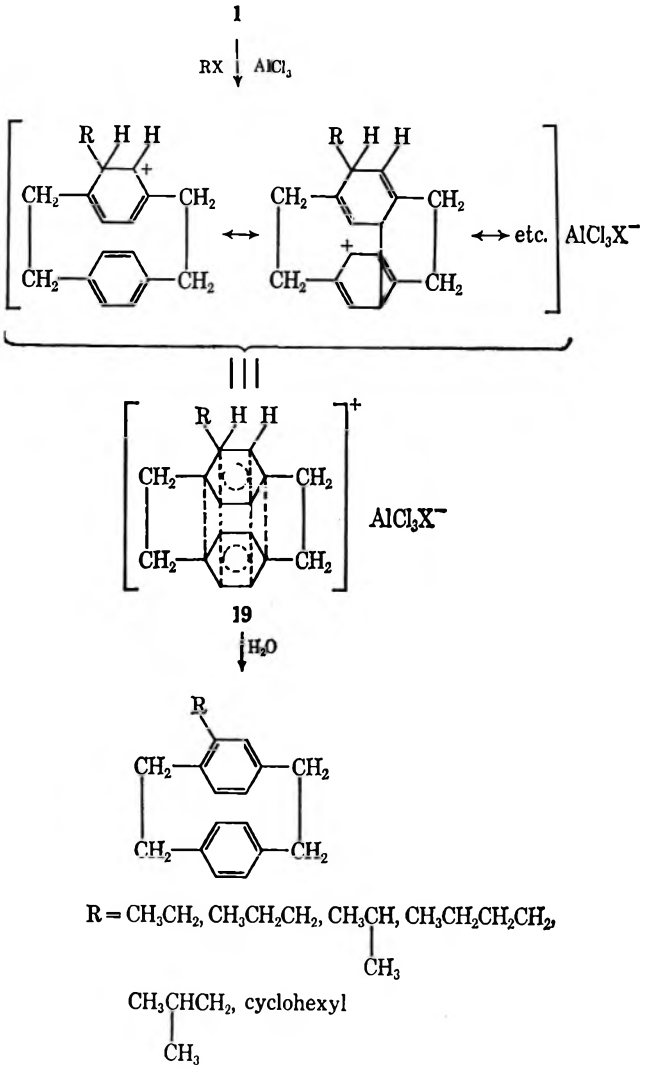
SCHEME II



(20) H. J. Reich and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 3078 (1967).
(21) W. F. Gorham (Union Carbide Corp.), U. S. Patent 3,117,168 (1964).

In order to account for this interesting stepwise alkylation, the formation of a stable carbonium ion complex **19** as an intermediate is postulated (Scheme III).

SCHEME III



The inital carbonium ion formed by the attack of the alkyl cation is stabilized, *via* transannular interaction, by both benzene rings, thus inhibiting further attack by available alkyl cations. Hydrolysis of **19** leads to monoalkyl[2.2]paracyclophane.

Experimental Section

General Procedure for Halogenation of [2.2]Paracyclophane.—Ring chlorination and bromination of [2.2]paracyclophane were carried out in a three-necked flask equipped with a gas inlet tube (for chlorination) or an additional funnel (for bromination), a mechanical stirrer, a reflux condenser, a thermometer, and a drying tube connecting to a gas trap. [2.2]Paracyclophane, a solvent (carbon tetrachloride or methylene chloride), and a small amount of catalyst (iron powder or Lewis acid) were placed in the flask and the mixture was heated to the reaction temperature of 25–50° with vigorous stirring. A stoichiometric amount of chlorine (or bromine) was added slowly to the reaction mixture. The addition should be completed in 1–3 hr depending on the amount of the halogen to be introduced. The mixture was digested for additional 15 min after the completion of the halogen addition. The catalyst was removed either by activated charcoal or by hydrolysis with water. The organic solution was filtered and the filtrate was concentrated to dryness. The crude

solid thus obtained was bulk distilled at 200–250° (0.5 mm) to yield a halogenated product in nearly quantitative yield.

4,16-Dichloro[2.2]paracyclophane (5).—Dichlorination of [2.2]paracyclophane was carried out according to the general procedure. [2.2]Paracyclophane (200 g), chlorine gas (140 g), iron powder (1 g), and methylene chloride (400 ml) were used in the chlorination. The dichlorinated product (255 g, 96%) was subjected to repeated recrystallization from hot ethanol to yield 56 g (21% of the dichlorinated product) of **5**, mp 212–213°.

Anal. Calcd for $C_{16}H_{14}Cl_2$: C, 69.31; H, 5.05. Found: C, 69.10; H, 5.06.

4,16-Dibromo[2.2]paracyclophane (6).—Dibromination of [2.2]paracyclophane was carried out according to the general procedure. [2.2]Paracyclophane (5 g), bromine (10 g), iron powder (0.1 g), and carbon tetrachloride (400 ml) were used in the bromination. The reaction was carried out at 40–50°. The dibrominated product (8 g, 91%) was subjected to repeated recrystallization from hot ethanol to yield 2.2 g (20% of the dibrominated product) of **6**, mp 245–246°.

Anal. Calcd for $C_{16}H_{14}Br_2$: C, 52.44; H, 3.82. Found: C, 52.60; H, 3.85.

4,16-Dilithio[2.2]paracyclophane (7).—A mixture of 4,16-dibromo[2.2]paracyclophane (20 g) and dry benzene (1000 ml) was placed in a dry, three-necked flask equipped with a condenser (protected from moisture with a drying tube), a magnetic stirrer, a nitrogen (dry) gas inlet, and a serum cap injection port. The mixture was heated until a complete solution was obtained. A small quantity (0.05 g) of copper powder was added to the solution. *n*-Butyllithium (75 ml, 14–15% in *n*-hexane) was added through the serum cap injection port with a syringe. The resulting mixture was heated to reflux for 1 hr under a dry inert atmosphere and with good stirring. After the period, the milky mixture was allowed to cool to room temperature. The product *in situ* was used immediately for further reactions.

4,16-Dicarboxyl[2.2]paracyclophane (8).—The above reaction mixture containing 4,16-dilithio[2.2]paracyclophane (**7**) was poured into a beaker containing powdered Dry Ice (about 500 g). After being allowed to warm to room temperature, the mixture was extracted repeatedly with water until the organic layer became clear. The aqueous extracts were combined, filtered, and acidified with hydrochloric acid. The product which precipitated out as a white solid was collected, washed successively with water and ether, and then dried to yield 15.4 g (95% based on **6**) of the acid, mp >310°. The acid was only sparingly soluble in all the common solvents tested. The crude acid was not purified.

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.40; neut equiv, 148. Found: C, 72.70; H, 5.11; neut equiv, 153.

4,16-Dicarbomethoxy[2.2]paracyclophane (8a).—The diacid **8** (2 g) was refluxed in dry methanol (100 ml) in the presence of a few drops of concentrated sulfuric acid. After 1 hr, the mixture was concentrated to dryness under reduced pressure. The whole process was reported until all the starting diacid became soluble in boiling methanol. The crude diester obtained after concentration was washed with aqueous sodium bicarbonate and water, and dried. Sublimation followed by recrystallization from boiling methanol provided 2 g (91% based on **8**) of pure product, mp 200–201°.

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.07; H, 6.17. Found: C, 73.79; H, 6.25.

4,16-Dimethyl[2.2]paracyclophane (9).—To the previous reaction mixture containing 4,16-dilithio[2.2]paracyclophane (**7**) was added dry dimethyl sulfate (300 ml) slowly with a syringe through the serum cap. Instant generation of heat was observed and the temperature of the mixture rose to about 75°. The mixture was stirred for an extra 30 min. Water (500 ml) was added to the mixture with stirring. The benzene layer was separated from the aqueous layer, washed with another 250 ml of water, filtered, and concentrated to dryness. Excess dimethyl sulfate was removed from the residual solid by drying the solid under vacuum (0.05 mm) at room temperature. Recrystallization of the residual solid from ethanol gave 11.5 g (90% based on **6**) of pure compound, mp 182–183°.

Anal. Calcd for $C_{18}H_{20}$: C, 91.52; H, 8.48. Found: C, 91.37; H, 8.50.

4,16-Diiodo[2.2]paracyclophane (10).—Iodine (55.6 g) was added all at once to the reaction mixture containing 4,16-dilithio-[2.2]paracyclophane (**7**) with vigorous stirring. The resulting mixture was digested for 20 min. Excess iodine was removed by extracting the reaction mixture successively with 10% aqueous sodium thiosulfate solution (100 ml) and water. The organic layer was separated, filtered, dried (Na_2SO_4), and concentrated. Recrystallization of the residual solid from hot benzene gave 15 g (60% based on **6**) of pure **10**, mp 272–273°.

Anal. Calcd. for $C_{16}H_{14}I_2$: C, 41.75; H, 3.04. Found: C, 41.89; H, 3.24.

4-Bromo-16-carboxy[2.2]paracyclophane (13).—To a mixture of 4,16-dibromo[2.2]paracyclophane (6 1 g) in dry ether (100 ml) was added *n*-butyllithium solution (4 ml, 14–15% in *n*-hexane) and a catalytic amount (0.05 g) of copper powder under anhydrous and inert atmosphere. The mixture was stirred at room temperature for 30 min. The mixture was then poured into powdered Dry Ice (10 g) and allowed to warm to room temperature. Water (25 ml) was added, and the organic layer was extracted a few times more with water. The aqueous extracts were combined, filtered, washed with ether, and then acidified with dilute hydrochloric acid. The precipitate was collected and washed with water and ether to yield 0.48 g (50%) of crude **13**, mp 285–287°. Attempts to recrystallize **13** produced only noncrystalline white powders.

Anal. Calcd for $C_{17}H_{15}O_2Br$: C, 61.60; H, 4.52; Br, 24.15; neut equiv, 331. Found: C, 61.21; H, 4.30; Br, 24.09; neut equiv, 355.

13 was converted into the methyl ester, mp 151–153°, by direct esterification with methanol.

4,16- and 8,16-Dicyano[2.2]paracyclophanes (14 and 15).—A mixture of 4,16-dibromo[2.2]paracyclophane (**6**) (7.32 g), dry cuprous cyanide (4.5 g), and freshly distilled dry quinoline (20 ml) was heated to 230–240° under a dry and inert atmosphere with good stirring for 20 hr. After the reaction period, the mixture was cooled to 100° and poured into a mixture of 10% aqueous ammonium hydroxide (100 ml) and benzene (100 ml). The resulting mixture was shaken well in a separatory funnel until all the lumps disintegrated. The benzene layer was separated, washed successively with two 100-ml portions of 10% aqueous ammonium hydroxide and water, filtered, and concentrated. The residual product was sublimed (180°, 0.05–0.10 mm) and recrystallized from ethanol to yield 4.15 g (81%) of a white crystalline product: mp 165–167°; ir (Nujol) 2225 (S, C≡N); vpc (silica gel) indicated the presence of two isomers in equal amount. Repeated recrystallization of the isomer mixture from ethanol–benzene (50/50) yielded a small amount (≤1%) of the less soluble isomer **14**, mp 233–235°.

Anal. Calcd for $C_{18}H_{14}N_2$: C, 83.72; H, 5.43; N, 10.85. Found: C, 83.45; H, 5.70; N, 10.54.

4-Ethyl[2.2]paracyclophane (16).—A mixture of aluminum chloride (3.4 g), *sym*-tetrachloroethane (50 ml), and ethyl bromide (8.5 ml) was cooled to −15° under anhydrous atmosphere with stirring. To the cooled mixture was added pulverized [2.2]paracyclophane (2.6 g). The deep purple-red mixture was stirred at −10 to −15° for 1 hr. After the period, the mixture was cooled to −30°. Dilute hydrochloric acid (1 *N*, 15 ml) was added dropwise to the mixture with vigorous stirring. The mixture was allowed to warm to room temperature while stirring. The organic layer was separated, washed successively with aqueous sodium bicarbonate and water, and dried (Na_2SO_4). Evaporation of the clear organic solution yielded a crude product which contained a small amount of the unreacted starting material. The crude product was dissolved in *n*-heptane (10 ml) and the insoluble [2.2]paracyclophane was removed by filtration. After removing *n*-heptane, the crude product was purified by sublimination followed by recrystallization from ethanol to give 2.5 g (85%) of **16**, mp 110–111°. A small portion of the product was recrystallized from ethanol to give an analytically pure sample, mp 111–112°.

Anal. Calcd for $C_{18}H_{20}$: C, 91.53; H, 8.47. Found: C, 91.51; H, 8.54.

Diethyl[2.2]paracyclophanes (17 and/or 18).—The procedure used in this preparation starting with 4-ethyl[2.2]paracyclophane (**16**, 2.5 g) together with aluminum chloride (3.4 g), ethyl bromide (8.5 ml), and *sym*-tetrachloroethane (50 ml) was identical with the procedure used for the preparation of **16** except for the purification step. After the removal of *sym*-tetrachloroethane, the residual product was distilled under reduced pressure. The distillate, a colorless viscous oil weighing 2.8 g (85%), was analyzed by vpc. It was composed of 68% **17** and/or **18** (broad peak) and 29% starting **16**. A small sample of pure product was isolated from vpc for elemental analysis. Attempts to crystallize the product were not successful.

Anal. Calcd for $C_{20}H_{24}$: C, 90.90; H, 9.09. Found: C, 90.72; H, 9.30.

Diethyl[2.2]paracyclophane was pyrolytically polymerized to give poly(ethyl-*p*-xylylene) by the general procedure described by Gorham.[4]

Registry No.—**5**, 10366-05-9; **6**, 5628-17-1; **7**, 19978-44-0; **8**, 19978-03-1; **8a**, 19978-04-2; **9**, R-CH_3, 10366-08-2; **10**, 19978-46-2; **13**, 19978-47-3; **13** methyl ester, 19978-48-4; **14**, 19978-49-5; **16**, 16070-18-1.

Bromination Reactions on Adsorbent Surfaces[1]

STEPHEN H. STOLDT AND AMOS TURK

Department of Chemistry, The City College of the City University of New York, New York, New York 10031

Received August 26, 1968

Bromination of cyclohexene and *cis*- and *trans*-2-butenes on activated carbon is exclusively a *trans* addition. Experimental conditions and results imply that the bromination is a surface reaction. It is suggested that the exclusive *trans* product results from mobility of Br ions on the carbon surface or from the steric constraint imposed by the pores of the adsorbent. Bromination of aromatic hydrocarbons by surface reactions gives ring substitution with a distribution of isomers that depends on the polarity, but not the pore sizes, of the adsorbent. Results are interpreted in the light of steric factors governing accessibility of adsorbed bromine to the aromatic ring.

Brominated activated carbon (BAC) is known to be effective in removing ethylene from air;[2] the action is addition followed by adsorption of the adduct by the carbon.[3] BAC has been used in air purification systems to protect fruit[2] and flowers[4] against the deleterious effects of small concentrations of atmospheric ethylene. These circumstances and the thought that the reaction environment of an adsorbent surface might produce some results different from those occuring in solution led us to the present study of bromination reactions on activated carbon and other adsorbents.

Addition.—The products, kinetics, and stereochemistry of the reaction of bromine with olefins have been extensively studied,[5] and the two-step *trans*-1,2 addition in liquid phase is well known. There are reported examples of *cis* chlorination,[6] but they all involve intermediates capable of existing as stable classical carbonium ions, and probably do not involve broadside approach of the Cl_2 molecule to the double bond. Moreover, since the ability of Cl to bridge two adjacent carbon atoms is markedly less than that of Br, a chloronium ion intermediate and its stereochemical consequences ought to be less important in chlorination than the bromonium ion in bromination. If *cis* bromination were to be successful, a process involving a broadside approach of Br_2 might be promising.

We studied the stereochemical course of addition of bromine to cyclohexene and to *cis*- and *trans*-2-butenes when the reactions occurred at the surfaces of activated carbon or silica gel. For each of these olefins, *cis* and *trans* addition would give different products.

Substitution.—The reaction of bromine with alkylbenzenes uncatalyzed by Lewis acids shows a high intermolecular and intramolecular selectivity (Table I). In all cases shown, the rate of bromination of alkylbenzene is high, and *ortho/para* substitution is observed almost exclusively. Where different relative rates are shown for a particular alkylbenzene they may be attributed to different methods of measurement. Differences in product distributions may be due to different methods of analysis and/or different reaction conditions. In all cases, the attacking reagent is most likely molecular bromine and not an ionic species.

The results of studies of bromination of toluene catalyzed by Lewis acids under nonisomerizing conditions appear in Table II. Zinc chloride in acetic acid gives high intermolecular selectivity as a bromination catalyst, but isomer distribution was not reported.[7] Ferric chloride in nitromethane gives bromination with a low substrate but high positional selectivity.[8] Olah concluded that the substrate-determining step involves a transition state similar to a π complex, but the product-determining step involves σ-complex-type transition states with corresponding high *ortho/para* selectivity. The higher proportions of *ortho* substitution than those found for molecular brominations[7-9] were explained as the result of attack by the incipient bromonium ion, a group with small steric requirements compared with molecular bromine.

The increase in substrate selectivity and decrease in the *ortho/para* ratio with increasing dilution indicate that increasing solvation makes the electrophile weaker and bulkier.[8]

Complexing of either aromatic hydrocarbon[9] halogen[8,10] or attacking with the solvent decreases the *ortho/para* ratio. Adsorption of the halogen on a surface should increase its effective bulk and therefore also decrease the *ortho/para* ratio. Adsorption of the aromatic hydrocarbon, on the other hand, can either increase or decrease this ratio depending on the relative geometry between the hydrocarbon and the surface.

We studied the bromination of toluene, cumene, and *t*-butylbenzene adsorbed on alumina, silica gel, and activated carbon, to determine the resulting isomer distributions and to evaluate them in terms of steric and/or electronic factors.

Indication of Reaction at the Surface.—To support

(1) Abstracted from the Ph.D. Thesis of S. H. S., The City University of New York, 1968.

(2) R. M. Smock, *Proc. Am. Soc. Hort. Sci.*, **44**, 134 (1944).

(3) A. Turk, J. I. Morrow, P. F. Levy, and P. Weissman, *Int. J. Air Water Pollution*, **5**, 14 (1961).

(4) C. W. Fischer, *Proc. Am. Soc. Hart. Sci.* **55**, 447 (1950).

(5) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," American Elsevier Publishing Co., New York, N. Y., 1966, Chapter 7.

(6) R. C. Fahey and C. Schubert, *J. Amer. Chem. Soc.*, **87**, 5172 (1965); P. B. D. de la Mare, N. V. Klassen, and R. Koenigsberger, *J. Chem. Soc.*, 5327 (1964).

(7) L. J. Andrews and R. M. Keefer, *J. Amer. Chem. Soc.*, **78**, 4549 (1956).

(8) G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *ibid.*, **86**, 1039 (1964).

(9) A. Campbell and D. J. Shields, *Tetrahedron*, **21**, 211 (1965).

(10) L. M. Stock and A. Himoe, *Tetrahedron Lett.*, 9 (1960).

TABLE I
MOLECULAR BROMINATION OF BENZENE AND MONOALKYLBENZENES

Aromatic (ArH)	Reaction condition	k_{ArH}/k_B	% ortho	% meta	% para	Method of analysis[a]	Ref
Benzene (B)	b	1					
Toluene	b	340	31		69	id	c
	b	605	32.9	0.3	66.8	ir	d
	e		41.5		58.5	oxidn	f
Ethylbenzene	b	290					c
	e		18		82	oxidn	f
Cumene	b	180					c
	e		11		89	oxidn	f
t-Butylbenzene	b	110	8		92	id	c
	b	138	1.20	1.47	97.3	ir	g

[a] id, isotope dilution; ir, infrared analysis. [b] In 85% HOAc (aqueous), 25°. [c] P. W. Robertson, P. B. D. de la Mare, and B. E. Swedlund, *J. Chem. Soc.*, 782 (1953). [d] H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.*, 79, 1421 (1957). [e] Neat in excess ArH, 45°. [f] I. N. Nazarov and A. V. Semenovskii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 840 (1957). [g] L. M. Stock and H. C. Brown, *J. Amer. Chem. Soc.*, 81, 5615 (1959).

TABLE II
LEWIS ACID CATALYZED BROMINATION OF TOLUENE

Solvent	Catalyst, concentration, M	Br_2, M	k_T/k_B[a]	% ortho	% meta	% para	Ref
CH_3COOH	$ZnCl_2$, 0.1	0.0019	148				b
CH_3NO_2	$FeCl_3$, 3.0	1.5	3.6	68.7	1.8	29.5	c
CH_3NO_2	$FeCl_3$, 0.1	0.05	32	58.4	~1	40.6	c

[a] T, toluene; B, benzene. [b] Reference 7. [c] Reference 8.

the likelihood that bromination of alkenes did occur at the surface and not during the recovery procedure, which consisted of extraction with carbon tetrachloride, the following experiments were performed.

A sample of brominated carbon was treated with a slight excess of an olefin (A) (in the case of ethylene a large excess was used). After 24 hr an equivalent quantity of a second olefin (B) was added, and the carbon was extracted with carbon tetrachloride. For each pair of olefins used, a second reaction was carried out in which the order of addition of the olefins was reversed. In this way any differences in the composition of any products formed during extraction which would be caused by differences in olefin reactivities could be assessed. The composition of the carbon tetrachloride solution was determined by gas chromatography and/or infrared (ir) spectroscopy. The results are summarized in Table III.

TABLE III
RESULTS OF SEQUENTIAL ADDITION OF OLEFINS TO BROMINATED CARBON

Starting olefins		Products	
A	B	A dibromide, %	B dibromide, %
Ethylene	*cis*-2-Butene	>99	<1
cis-2-Butene	Ethylene	99	1
cis-2-Butene	Cyclohexene	99	1
Cyclohexene	*cis*-2-Butene	99	1

If bromination of olefins is a surface reaction, the product should, in each case, be mainly or exclusively the bromination product of olefin A (A dibromide in Table III). If reaction occurs in solution during extraction, however, the olefins will compete and the products in each case will be determined by the relative reactivities of the two olefins toward bromine or, if the reaction is diffusion controlled, by the relative availabilities of the olefins. In either of these latter cases the order of addition of olefins should have no effect on product ratios.

The data in Table III indicate that reaction does occur at the surface, since the first-added olefin (A) in every case gives the predominant product.

If bromination of olefins occurred before recovery but not at the surface (that is, in the vapor phase and/or by capillary condensation of reactants), allylic and addition–elimination bromination reactions would be likely to compete with addition, as they do in vapor or liquid phase brominations without an adsorbent. While no B dibromide would be observed, such products as 1-bromo-2-butene, 3-bromo-1-butene, 2-bromo-2-butene, 1- and 3-bromocyclohexenes and their bromine addition products should also have been found. The absence of all products except those of direct bromine addition argues strongly against the occurrence of an appreciable reaction in the liquid or vapor phase in competition with reaction of adsorbed species.

Furthermore, in the case of bromination of aromatic compounds, work done on the vapor phase thermal and photochemical brominations of toluene shows mainly formation of benzyl bromide.[11] Therefore, in the present study in which nuclear bromination is observed, the reaction is a surface, not a vapor phase reaction. (The possibility of the occurrence of a competing vapor phase reaction to give benzyl bromide is not excluded, but such reaction will not interfere with the nuclear bromination at the surface.)

Experimental Section

Bromination Procedures.—Brominations were carried out in a high-vacuum system which has been previously described.[3] The following is typical of all of the brominations of aromatic compounds.

Carbon (Table IV) (55 g) was cleaned by heating *in vacuo* at 460–480°. Toluene (*ca.* 5 ml) was placed in the adjacent trap, the trap was evacuated until 4.0 ml (3.5 g, 38 mmol) of toluene remained, and the toluene vapors were allowed to diffuse onto the carbon. The glass oven containing the carbon was then sealed off and heated at 176° for 2 hr to distribute the toluene evenly over the surface; then it was cooled slowly.

Bromine (0.560 ml, 1.75 g, 10.9 mmol; stored over anhydrous potassium carbonate before use) was transferred under dry nitrogen to the reserve trap. The bromine was degassed by successively cooling (−78°), evacuating, warming, cooling, and evacuat-

(11) H. R. Anderson, Jr., H. A. Scheraga, and E. R. van Artsdalen, *J. Chem. Phys.*, 21, 1258 (1953).

TABLE IV
PROPERTIES OF CARBONS (SOURCE: COCONUT SHELLS)[a]

Manufacturer's[b] designation of carbon	Total surface area,[c] m^2/g	Most[d] common pore size, Å	Pore[d] volume, cm^3/g
JD-1	1000–1100		
K-3030	1000–1100	10–20	0.433
K-3031	500–600	10–15	0.335
K-3032	1600–1700	15–25	0.513

[a] A. Turk, J. I. Morrow, S. H. Stoldt, and W. Baecht, *J. Air Pollution Control Assoc.*, 16, 383 (1966). [b] Barnebey-Cheney Co., Columbus 19, Ohio. [c] B. E. T. method. [d] By mercury porosimeter.

ing. The frozen bromine *in vacuo* was finally allowed to warm and to distil through the system into the trap (cooled to −78°) adjacent to the reaction vessel. This trap was then warmed to and held at −12°, and the bromine was allowed to diffuse slowly into the reaction vessel which had been wrapped with aluminum foil to prevent light-induced reactions. Addition of bromine required 3 hr.

After 8 days the vacuum system was flushed three times with ethylene, with intermittent evacuations, and then filled with ethylene which was added in small portions to the reaction vessel. The cycle of filling the system with ethylene and passing the ethylene into the reaction vessel was repeated until the pressure of ethylene within the system approximated atmospheric pressure. The reaction vessel was allowed to stand for 2 days to ensure complete reaction of the ethylene with any free bromine.

Most of the ethylene was desorbed *in vacuo* at room temperature into a trap cooled in liquid nitrogen. The oven was closed off and the liquid nitrogen was replaced with Dry Ice–acetone to distil the collected ethylene off through the system while retaining any higher boiling materials. The liquid nitrogen bath was then replaced, and the material in the oven was desorbed at successively increasing temperatures over various periods of time, as indicated for a typical experiment in Table V. Correspondingly higher temperatures were used when the alkylbenzene was of higher molecular weight.

TABLE V
DESORPTION CONDITIONS AFTER BROMINATION OF TOLUENE

Minutes desorbed	Temperature, °C
15	Ambient
60	77
60	168
75	239
60	279
80	385

The liquid nitrogen was replaced with Dry Ice–acetone, and the ethylene was again distilled off. After the trap was warmed to room temperature, its contents were removed by pipet and washed twice with aqueous sodium bromide, once with 2 *M* sodium hydroxide, and twice with aqueous sodium bromide.

The organic layer was analyzed by glpc. The bromotoluene isomers were partially separated on a 12 ft × ½ in. neopentyl glycol succinate column (25% on 60/80 mesh Chromosorb P) at 112°, 240 cc of helium/min. Under these conditions the *o*-bromotoluene was cleanly separated from the *meta* and *para* isomers, which emerged together. Analyses of standard mixtures showed that the responses of the isomers were identical within experimental error, and therefore the relative areas were used as direct measures of isomer distribution. Infrared analysis of the product mixtures and of standard mixtures showed that in all reactions the *meta* isomer was present to the extent of less than 1%. The results are summarized in Table VI.

Reactions of bromine with olefins were conducted similarly. The olefin, if a gas, was added by the procedure described earlier for ethylene. If the olefin was a liquid, it was added as were the aromatic hydrocarbons. When it was necessary to know the exact molar quantity of gaseous olefin used, a bulb of known volume sealed onto the vacuum system was employed. Addition of bromine as described above required 4.5 hr.

The instability of vicinal dibromoalkanes compared with aryl bromides necessitated milder methods of recovery and analysis. Thus, after 2 days reaction time the carbon was transferred to

TABLE VI
RESULTS OF RING BROMINATION OF AROMATIC HYDROCARBONS AT ADSORBENT SURFACES

Run no.	Adsorbent[a]	Hydrocarbon	Bromine added before or after hydrocarbon	Scavenger	% *ortho*[b]
1	C, JD-1[c]	Toluene	Before	None	64.5
2	C, JD-1	Toluene	After	Ethylene	48.8
3	C, JD-1	Toluene and benzene[d]	After	Ethylene	*e*
4	C, JD-1[f]	Toluene[g]	After	Ethylene	52.2
5	C, K-3030[c]	Toluene	After	Ethylene	52.3
6	C, K-3031[c]	Toluene	After	Ethylene	52.1
7	C, K-3032[c]	Toluene	After	Ethylene	51.8
8	S	Toluene	Before	Ethylene	36.2
9	S	Toluene	After	Ethylene	37.9
10	A	Toluene	After	Ethylene	27
11	C, JD-1	Cumene	After	Ethylene	28.2
12	C, JD-1	*t*-Butylbenzene	After	Ethylene	0

[a] C, activated carbon; S, silica gel; A, activated alumina. [b] The rest was *para*, the *meta* isomer being negligible in all cases. [c] Designation by manufacturer, Barnebey-Cheney Co., Columbus, Ohio. See Table IV for properties. [d] Competition experiment. [e] Not determined. [f] The carbon was acid washed prior to the experiment. [g] Toluene "from sulfonic acid" (Eastman-Kodak).

a Soxhlet extractor and extracted for 7.5 hr with carbon tetrachloride. The solution was concentrated (rotary evaporator), and the residue was analyzed by ir and/or nmr spectroscopy.

2-*o*-Bromophenyl-2-propanol (I).—This was prepared from 15.05 g (0.070 mol) of methyl *o*-bromobenzoate according to the method of Stiles and Sisti,[12] except that methyl iodide was used instead of methyl bromide for the Grignard reagent. Distillation under reduced pressure yielded a slightly yellow liquid: bp 68–73° (0.37 Torr). This crude alcohol was used directly in the preparation of *o*-bromocumene.

***o*-Bromocumene (II).**—Crude I was hydrogenated over 5% Pd–C in AcOH acidified with $HClO_4$.[12] After filtration and removal of acetic acid at reduced pressure, the residual oil was extracted with aqueous $NaHCO_3$ and steam distilled to give 9.5 g (68% over-all yield) of a clear, colorless oil. Distillation under reduced pressure yielded a clear colorless liquid: ir (liquid film) 3050 (w, aromatic H), 2960, 2900, 2840 (m, alkyl H), 1590, 1560 (w, aromatic), 1470 (m, methyl), 1420 (m, methine), 1370, 1350 (w, isopropyl), 756 cm^{-1} (s, *ortho*-disubstituted benzene); nmr (CCl_4) δ 1.23 (doublet, J = 7 cps, 6 H, methyl), 2.73 (septuplet, J = 7 cps, 1 H, methine proton), 6.9–7.3 (complex, 4 H, aromatic).

***m*-Bromocumene (III).**—This was prepared similarly to the *ortho* isomer[12] as a clear colorless liquid: ir (liquid film) 3030 (w, aromatic H), 2940 (s), 2910, 2850 (m, alkyl H), 1595, 1570 (m, aromatic), 1475, 1455 (m, methyl), 1418 (m, methine), 1377, 1357 (w, isopropyl), 778, 691 cm^{-1} (s, *meta*-disubstituted benzene); nmr (CCl_4) δ 1.21 (doublet, J = 7 cps, 6 H, methyl), 2.82 (septuplet, J = 7 cps, 1 H, methine proton), 6.98–7.40 (complex, 4 H, aromatic).

Results and Discussion

Olefins.—Bromination of olefins by BAC, under conditions such that the reaction occurred at the surface, led exclusively to the products formed by *trans* addition. Analysis by nmr spectroscopy, utilizing the chemical shifts of the methine protons and the splitting patterns of the methyl protons,[13] showed that *cis*-2-butene gave exclusively *dl*-2,3-dibromobutane and that *trans*-2-butene gave only the *meso* isomer. Comparison of the ir spectra of the 1,2-dibromocyclohexanes obtained in these reactions with the spectra of *cis*- and

(12) M. Stiles and A. J. Sisti, *J. Org. Chem.*, **25**, 1691 (1960).
(13) F. A. L. Anet, *Proc. Chem. Soc.*, 327 (1959).

trans-1,2-dibromocyclohexanes[14] showed that only the *trans* isomer was produced. These results are independent of the order of addition of reactants. Variation of the bromine concentration on the charcoal between 1 and 10% by weight had no effects on the products nor, in the case of cyclohexene, did the use of silica gel in place of carbon. These reactions gave no detectable quantities of side products, in contrast to brominations in solution in which allylic substitution reactions compete with addition.[15,16]

The reason for these results is unclear. In every experiment the ratio of quantity of reactant to surface area of adsorbent was less than that required to yield a theoretical molecular monolayer, and capillary condensation with consequent liquid phase reaction was therefore unlikely. One possible mechanism involves a two-step surface process like that in solution, with formation of a bromonium (or β-bromocarbonium) ion and a bromide (or possibly tribromide) anion. Such a process would require mobility of a least one of the ions on the surface to give backside attack and over-all *trans* addition.

Alternatively, the steric constraint imposed by the pores in the adsorbent could facilitate the bridging of a series of Br_2 molecules, possibly through dipole-induced dipole interactions, around the olefin molecule until *trans* addition occurs. The involvement of a pore of an adsorbent with two sides of a molecule has recently been postulated for another reaction.[17] The large number of bromine molecules necessarily involved in such a pathway may be plausible in light of the facts that bromination of unreactive olefins in acetic acid has been shown to be third order in bromine in the region of bromine concentrations of 0.1–0.2 M[18] and that the effective concentration of bromine molecules at the adsorbent surface may be considerably greater than this value. Moreover, the mobility of the adsorbed molecules is reduced relative to the mobility of these molecules in solution. For these reasons the involvement of a large number of bromine molecules in bromination of an olefin at an adsorbent surface is not at all unlikely.

Any mechanism involving free radicals may be dismissed as highly unlikely since no products which would be associated with such a mechanism could be detected.

Aromatic Hydrocarbons.—The bromination of toluene at adsorbent surfaces, using ethylene as a scavenger, gave yields of combined bromotoluene isomers approximating 50% (based on Br_2), the remainder of the desorbate being $C_2H_4Br_2$ and unreacted toluene. With cumene, the combined yield of products from side-chain bromination, $C_6H_5C(CH_3)_2Br$ and $C_6H_5C(CH_3)=CH_2$, was the major part of the product mixture. Table VI gives the distribution of isomers from ring bromination for different experiments.

The results or runs 1 and 2 showed that bromination of toluene at the carbon surface is not complete after 8 days. When ethylene was added (run 2) and the products were vacuum desorbed at high temperatures, significant quantities of ethylene bromide were formed, and the bromotoluenes consisted of 49% *ortho* isomer. When the carbon was vacuum desorbed after reaction without ethylene being added, the bromotoluenes consisted of 64.5% *ortho* isomer, and much benzyl bromide was formed. These data indicate that, if no ethylene is used, reaction occurs both on the surface and in the vapor phase at the high temperatures required for the vacuum desorption. The reaction in the vapor phase will lead to benzyl bromide.[11] The higher temperature reaction at the surface will of course be much more rapid and less selective, and the *ortho*/*para* ratio should be closer to statistical than at ambient temperatures, as is observed.

The low proportion of *meta* bromination (<1%) in these and in all other brominations of alkylbenzenes studied indicates high selectivity, kinetic control, and no subsequent equilibration of products.

A sample of *p*-bromotoluene was adsorbed on activated carbon, left 8 days, and desorbed using the same procedure as was employed for the products of bromination reactions. No alteration of the sample occurred. Olah showed that *p*-bromotoluene isomerizes faster under the influence of aluminum chloride than either the *ortho* or *meta* isomer.[19] Therefore, the products obtained from the surface reactions are determined by kinetic control of the reaction and not by any secondary transformations of products.

This high selectivity is also intermolecular. A competition between equimolar quantities of benzene and toluene for a limited quantity of bromine (run 3) gave no detectable bromobenzene by gas chromatography, indicating a substrate selectivity of toluene over benzene by a factor of at least 100 since 1% of bromobenzene in the products could easily have been detected.

When a sample of carbon which has been cleaned *in vacuo* at high temperatures is mixed with water, the pH of the water rapidly rises to 10, indicating the presence of nonvolatile basic impurities on the carbon. To determine their possible effect on the course of bromination, a sample of carbon was extracted with aqueous hydrochloric acid, washed with water, dried, and cleaned *in vacuo* as usual. Use of this carbon (run 4) produced no change in the isomer distribution in the bromination of toluene.

Runs 5–7 show that different pore structures and surface areas have no effect on isomer distributions. The properties of these carbons are shown in Table IV.

In all these cases it can be seen that the *ortho*/*para* ratio is larger than for the uncatalyzed reaction of toluene and bromine in 85% acetic acid[8] and that it is insensitive to several variable properties of the charcoal surface.

When neutral silica gel was used as adsorbent (runs 8 and 9), the bromination of toluene appeared to resemble more closely the same reaction in solution. Thus, Brown and Stock found 33% *ortho* and 67% *para* bromination of toluene in 85% acetic acid.[8] Bromination on silica gel gave 37% *ortho* and 63% *para* substitution. These results could be caused by the more polar adsorbent (silica gel) being better able to stabilize ionic intermediates and/or by the toluene being less strongly adsorbed on the silica gel than on carbon and thus in a condition sterically resembling more

(14) H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Amer. Chem. Soc.*, **74**, 3588 (1952).
(15) C. D. Hurd and L. U. Spence, *ibid.*, **51**, 3561 (1929).
(16) J. Wolinsky and K. L. Erickson, *J. Org. Chem.*, **30**, 2208 (1965).
(17) E. J. Blanc and H. Pines, *ibid.*, **33**, 2035 (1968).
(18) B. E. Swedlund and P. W. Robertson, *J. Chem. Soc.*, 630 (1947).
(19) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **27**, 3464 (1962).

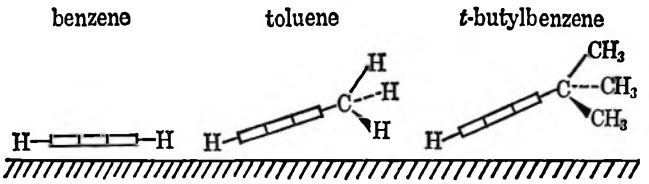


Figure 1.—Possible geometries of adsorbed aromatic hydrocarbons.

closely its condition in solution. These results also indicate the isomer composition of the bromotoluenes to be independent of the order of addition of the reactants.

Finally, bromination of toluene on neutral alumina (run 10) decreased still further the *ortho/para* ratio (27% *ortho*) probably for one or both of the reasons mentioned above for silica gel.

Cumene (run 11) gave 28.2% *ortho* bromination, also with <1% *meta* isomer. In this case side-chain bromination was actually the major process even in the dark, and large quantities of 2-bromo-2-phenylpropane and its dehydrobromination product, 2-phenylpropene, were formed. This is of course due to the α hydrogen in cumene being much more easily abstracted than those in toluene in the free-radical side-chain bromination. (This observation indicates that allylic substitution, probably *via* a free-radical mechanism, also is capable of occurring on the adsorbent surface.) With cumene, as with toluene, the *ortho/para* ratio is higher than for the same reaction in solution, in which 11% *ortho* and 89% *para* bromination are observed.[9]

t-Butylbenzene (run 12) gave completely *para* substitution. It appears that in this case the effect of the carbon surface, which is to increase *ortho* substitution in toluene and cumene, is insufficient to cause appreciable *ortho* substitution *t*-butylbenzene.

The results may be interpreted in the light of the diagrams in Figure 1 and the calculated values in Table VII.

TABLE VII
DERIVED VALUES FROM TABLES I AND VI

Aromatic	*ortho/para*[a] (Brown)	*ortho/para*[b]	*ortho/para*[c]
Toluene	0.49	0.71	1.1
Ethylbenzene		0.22	
Cumene		0.12	0.40
t-Butylbenzene	0.012		~0

[a] Brown. [b] Reference 9. [c] This work.

Whereas the corner-to-corner C_2 axis of the aromatic ring of benzene can be completely parallel to the axis of the pore in which it is absorbed (the pore is assumed to be approximately cylindrical), the methyl substituent in toluene can prevent the C_2 axis of this aromatic ring from attaining parallelism with the axis of the pore by preventing that end of the molecule to which it is attached from approaching the surface as closely as can the other end of the molecule. The position *para* to the methyl group in toluene can therefore approach the surface more closely than can the positions *ortho* to the methyl group. The hindrance resulting from the presence of the surface will be correspondingly greater in the *para* than in the *ortho* position. Such a situation would lead to the expectation that the *ortho/para* ratio for bromination of toluene at a surface might be greater than that in solution (neglecting solvent effects). This has been shown in the present work to be true (Table VII).

As the alkyl substitutent becomes more bulky the departure of the C_2 axis of the adsorbed aromatic ring from strict parallelism with the axis of the pore should increase. The hindrance cause by the surface at the *para* position relative to that at the *ortho* position should also increase as the C_2 axis of the aromatic compound is forced further from a geometry parallel to the axis of the pore.

Lack of a complete set of isomer distribution data for the series toluene, ethylbenzene, cumene, and *t*-butylbenzene under a uniform set of conditions makes a strict comparison of results tenuous. However, the data for toluene and cumene may be compared with the results of Nazarov and Semenovskii[9] (45°, excess aromatic hydrocarbon).

Division of the *ortho/para* ratio for bromination at the surface of activated carbon, 1.1, by the *ortho/para* ratio for liquid phase bromination at 45°,[9] 0.71, shows an increase in this ratio by a factor of 1.5. As predicted earlier, the relative increase in the *ortho/para* ratio for an alkylbenzene with a bulkier substituent than a methyl group should exceed that for toluene. For cumene, the *ortho/para* ratio at 45°[9] is 0.12. Dividing this value into the *ortho/para* ratio at activated carbon, 0.40, gives an enhancement of the *ortho/para* ratio by a factor of 3.3, more than twice the enhancement found for toluene. These results indicate the qualitative validity of the foregoing assumptions.

The data obtained for *t*-butylbenzene indicate the fraction of *ortho* substitution to be too low to make possible a similar comparison between Brown's results for toluene[8] and *t*-butylbenzene[10] and those found in the present work. Thus, *t*-butylbenzene does not follow the trend from toluene to cumene shown above. It may be that the *t*-butyl group is too bulky to allow *t*-butylbenzene to be adsorbed similarly to benzene, toluene, and cumene but with a geometry in which the C_2 axis is still further from being parallel with the axis of the pore.

Activated carbon is known to adsorb relatively nonpolar organic molecules more strongly than do the inorganic adsorbents silica gel and alumina. If an aromatic compound is less strongly adsorbed on silica gel or alumina than on activated carbon, the departure from parallel arrangements shown in Figure 1 should be lessened. Therefore the difference between the isomer distributions in bromination of toluene in solution and in the adosrbed state should also be lessened since the surfaces of silica gel and alumina will not preferentially hinder the *para* position relative to the *ortho* position as greatly as will the activated carbon surface. The *ortho/para* ratio for bromination of toluene at silica gel or alumina should therefore decrease from that for bromination at activated carbon and approach the value for the toluene molecule in solution unhindered by an adsorbent.

In addition, the presence of polar silicon–oxygen and aluminum–oxygen linkages in the inorganic adsorbents makes possible a greater stabilization of charges in adsorbed species than is found with activated carbon. Thus bromination at the surfaces of silica gel and

alumina should more closely resemble reaction in acetic acid solution, in which solvent has been shown to have a stabilizing effect on the ions, than will bromination at activated carbon.

Thus, two independent considerations predict that reaction on the inorganic adsorbents will more closely resemble that in solution than will reaction on activated carbon. Such has been shown to be the case; the *ortho/para* ratios for bromination of toluene at the surfaces of activated carbon, silica gel, and alumina are 1.1, 0.59, and 0.37, respectively, compared with 0.49 in 85% acetic acid[8] and 0.71 in excess toluene.[9] Bromination at the surface of alumina actually gives a lower *ortho/para* ratio than does bromination in 85% acetic acid.

The effect of interaction between bromine and the surface on isomer distributions must also be considered.

In chlorination of toluene in various solvents the *ortho/para* ratios varied from 2.2 in trifluoroacetic acid to 0.52 in nitromethane. The *ortho/para* ratio decreased as the complexing of chlorine with solvent increased.[10]

The differential heat of adsorption of bromine is 7719 cal/mol on silica gel and 11,430 cal/mol on activated carbon; the former value is only a few hundred calories above the heat of condensation of bromine.[20] If being held more tightly on the surface would increase the selectivity of bromine for the *para* position of toluene over the *ortho* positions, than the lowest *ortho/para* ratios should be obtained on activated carbon. Since the opposite was observed, the combination of steric and electronic effects of the surface on the aromatic hydrocarbon is probably more important in determining the course of attack than are the effects of the surface on the bromine.

Registry No.—Cyclohexene, 110-83-8; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; benzene, 71-43-2; toluene, 108-88-3; ethylbenzene, 100-41-4; cumene, 98-82-8; butylbenzene, 98-06-6; ethylene, 74-85-1.

Acknowledgment.—The work was supported by a research grant of the National Center for Air Pollution Control, U. S. Public Health Service. Stephen H. Stoldt was the recipient of an NDEA (Title IV) Fellowship, a NASA Traineeship, and City University of New York Research Assistantships.

(20) L. H. Reyerson and A. E. Cameron, *J. Phys. Chem.*, **39**, 181 (1935).

The Synthesis of Azulene-1-alkanoic Acids, Azulene-1,3-dialkanoic Acids, and Related Compounds. A 1,3-Bridged Azulene[1]

Arthur G. Anderson, Jr., and Robert D. Breazeale[2]

Department of Chemistry, University of Washington, Seattle, Washington 98105

Received October 31, 1968

1,3-Bis(2′,2′-dicarboxyethyl)azulene (2), azulyl-1,3-bis(propanoic acid) (3), 1,3-bis(2′-carbethoxy-3′-oxobutyl)azulene (4), 1,3-bis(3′-oxobutyl)azulene (5), diethyl azulene-1,3-dipropanoate (6), and 1,3-bis(3′-hydroxypropyl)azulene (7) have been synthesized *via* nucleophilic displacement reactions on azulyl-1,3-bis(methyltrimethylammonium) diiodide (1). Vilsmeier acylation reactions and reduction of the carbonyl groups in the 1-acylazulene products to methylenes by either the hydride reduction–alkylideneazulenium salt–hydride reduction method or, in one step, by diborane have been used to prepare 1-ethylazulene, ethyl 5-(1-azulyl)-5-oxopentanoate (8a), ethyl 5-(1-azulyl)pentanoate (10a), 1-(1′-oxo-4′-carbethoxybutyl)-3-(5′-chloropentyl)-azulene (11a), azulene-1,3-bis(hexanenitrile) (14a), ethyl 4-(1-azulyl)-4-oxobutanoate (8b), 1-(4′-chlorobutyl)-3-(1′-oxo-3′-carbethoxypropyl)azulene (11b), azulene-1,3-bis(pentanenitrile) (14b), 1,3-bis(1′-oxo-3′-carbomethoxypropyl)azulene (16), N,N-diethyl-10-(1-azulyl)decanamide (21), pentylazulene (22), 1,3-dipentylazulene (23), 1,3-dipropionylazulene (24), and 1,3-dipropylazulene (25). The principal maxima in the visible absorption spectra for the 1-alkyl- and 1,3-dialkylazulenes are compared. The diborane reduction of the acylazulenes is discussed. A high-dilution Thorpe–Ziegler ring closure of 14a gave 1,3-(5′-cyano-6′-oxoundecamethylene)azulene (26), the first example of a 1,3-bridged azulene. Attempts to form 1,3-bridged products from 14b, 21, and 6 were unsuccessful.

In the course of studies on azulene[3] it was desired to prepare the derivatives given in the title, in part because certain of these might lead to 1,3 bridging of the nonbenzenoid azulene structure and thus provide a novel example of this type of structure. The syntheses required the formation of a saturated methylene carbon attached to the ring and a suitable functional group at the other end of the chain. This paper describes the methods found to accomplish these objectives and the preparation of the first example of a 1,3-bridged azulene.

The direct introduction of a methylene carbon onto the 1 position of azulene had been found practical as a synthetic method only for aminomethylation[4-6] and, for certain cases, the reaction with aliphatic diazo compounds.[7] The former had provided the first step in pathways to azulene-1-ethanoic acid and azulene-1-propanoic acid,[4] and the latter afforded a direct route to ethyl azulene-1-ethanoate. Since the results of an attempt to form an azulene-1,3-dialkanoic acid ester by the acid-catalyzed decomposition of an ω-diazo ester in the presence of azulene were not promising, the displacement reactions of azulyl-1,3-bis(methyltrimethylammonium) diiodide (1) with the anions of active methylene compounds were tried (Scheme I). From 1 and diethyl sodiomalonate was obtained, after hydroly-

(1) Supported in part by a grant from the National Science Foundation. From the Ph.D. Thesis of R. D. Breazeale, University of Washington, 1964.

(2) Weyerhaeuser Fellow, 1962–1963.

(3) *Cf.* A. G. Anderson, Jr., and R. C. Rhodes, *J. Org. Chem.*, **30**, 1616 (1965), and preceding papers.

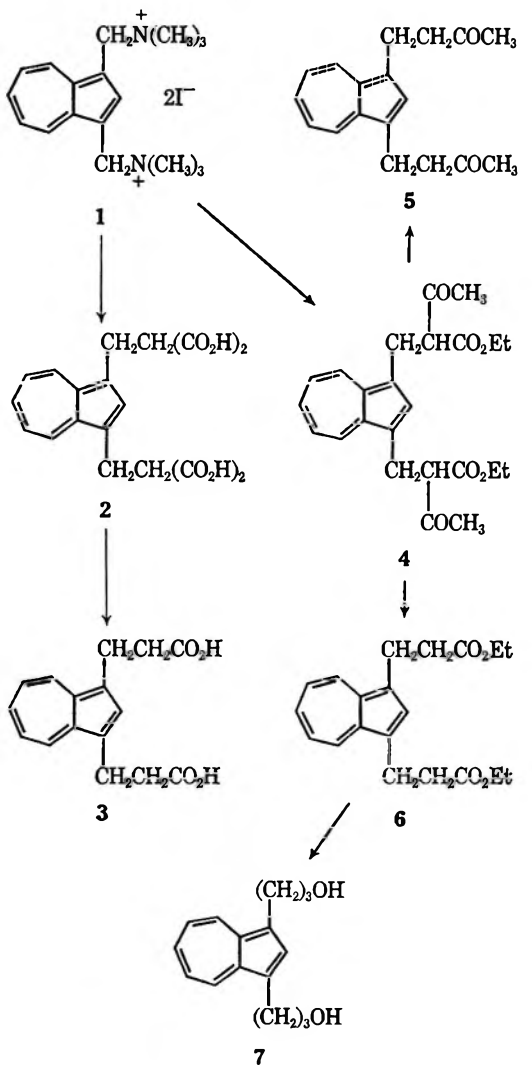
(4) A. G. Anderson, Jr., R. G. Anderson, and T. S. Fujita, *ibid.*, **27**, 4535 (1962).

(5) K. Hafner, *Angew. Chem.*, **70**, 419 (1958).

(6) M. Mühlstadt, W. Treibs, and J. Mohr, *Chem. Ber.*, **94**, 808 (1961).

(7) (a) A. G. Anderson, Jr., and R. C. Rhodes, *J. Org. Chem.*, **30**, 1616 (1965); (b) S. Hauptmann and K. Hirschberg, *J. Prakt. Chem.*, **34**, 272 (1966).

SCHEME I



sis, 1,3-bis(2′,2′-dicarboxyethyl)azulene (**2**, 86% yield). The decarboxylation of **2**, however, gave only 21% azulyl-1,3-bis(propanoic acid) (**3**). The direct displacement on **1** with sodium α-sodioacetate would circumvent the low yield decarboxylation, and precedent for the action of this anion as a nucleophile at a benzylic position was found in the formation of phenylpropanoic acid in good yield from benzyl chloride.[8] Although a variety of conditions was tried, the displacement by sodium α-sodioacetate on **1** did not occur. A possible reason is that the disodium salt was acting as a base on the diquaternary salt.[9]

Another anion investigated as a nucleophile was ethyl sodioacetoacetate, which had been used previously on the corresponding monoquaternary salt.[4] From the reaction with **1** followed by hydrolysis and acidification (decarboxylation occurred spontaneously) was obtained 1,3-bis(3′-oxobutyl)azulene (**5**) in 53% yield. An iodoform reaction with **5**, which had been used with success on 1-acetyl- and 1,3-diacetylazulene,[10] did not give **3**[11] and a different degradation of **4** was sought. The deacetylation of substituted acetoacetic esters in good yield had been reported by Ritter and Kaniecki[12] and the application of this method to 1,3-bis(2′-carbethoxy-3′-oxobutyl)azulene (**4**), formed in 80% yield, afforded a 69% yield of diethyl azulene-1,3-dipropanoate (**6**). Hydride reduction of **6** produced 1,3-bis(3′-hydroxypropyl)azulene (**7**) in high yield. As had been found earlier with 1-methylazulene, these 1,3-dialkylazulenes were unstable to atmospheric oxygen and good analyses were not obtained for some, although the spectral data were clearly consistent with the proposed structures.

The introduction of an unsaturated carbon with subsequent reduction to a methylene was the alternative possibility and a variety of reactions for the first step were available. The Vilsmeier reaction of N,N-dialkylamides and phosphorus oxychloride with activated aromatic compounds to give aryl aldehydes or ketones had been used effectively by Hafner[13] and Treibs[14] and coworkers, although the preparation of 1,3-diformylazulene was the only case of disubstitution reported.[13,14] This method and that of the more common acylation reactions offered potential means of forming azulyl alkyl ketones having the desired functional groups on the ω carbon.

Vilsmeier substitution with ω-carbethoxy-N,N-dialkylamides[15] was chosen for the synthesis of 1-(α-oxo-ω-carbethoxyalkyl)azulenes[7b] (Scheme II). Reaction of azulene with ethyl N,N-diethylglutaramate, prepared in 52% yield by the reaction of glutaric anhydride and diethylamine followed by esterification, gave an 86% yield of ethyl 5-(1-azulyl)-5-oxopentanoate (**8a**), and there remained the reduction step. Consideration of previous findings on the reduction of 1-acyl- and 1,3-diacylazulenes indicated that Wolff–Kishner,[13,14,16,17] Clemmensen,[16,17] or Raney nickel desulfurization[16,17] methods would not be satisfactory. Attention was therefore turned to other methods. Hafner, *et al.*,[18] had found that the alcohol formed by hydride reduction of an acylazulene was converted by 70% perchloric acid or anhydrous fluoroboric acid into an alkylideneazulenium salt, and this, in turn, was reduced by lithium aluminum hydride to an alkylazulene. In a model experiment 1-(α-hydroxyethyl)azulene, obtained by sodium borohydride reduction of 1-acetylazulene, was converted into 1-ethylazulene *via* a modification of the Hafner method (perchlorate salt) in 27% yield. The rather low yield realized led to the trial of boron trifluoride etherate and sodium borohydride which Pettit, *et al.*,[19] had used for the reduction of β-propionylnaphthalene and β-(1-hydroxypropyl)naphthalene to

(8) Technical brochure kindly provided by the Ethyl Corp. We also thank this company for a sample of the sodium α-sodioacetate.

(9) The sodium α-sodioacetate is a stronger base than amide ion and the latter had been found to give only polymeric material with **1**.

(10) A. G. Anderson, Jr., R. Scotoni, Jr., E. J. Cowles, and C. G. Fritz, *J. Org. Chem.*, **22**, 1193 (1957).

(11) The amount of acidic azulenic product was very small and other products were not identified.

(12) J. J. Ritter and T. J. Kaniecki, *ibid.*, **27**, 622 (1962).

(13) K. Hafner and C. Bernhard, *Ann.*, **625**, 108 (1959).

(14) W. Treibs, H. Neupert, and J. Hiebsch, *Chem. Ber.*, **92**, 141 (1959).

(15) A. W. D. Avison, *J. Appl. Chem.*, **1**, 469 (1951).

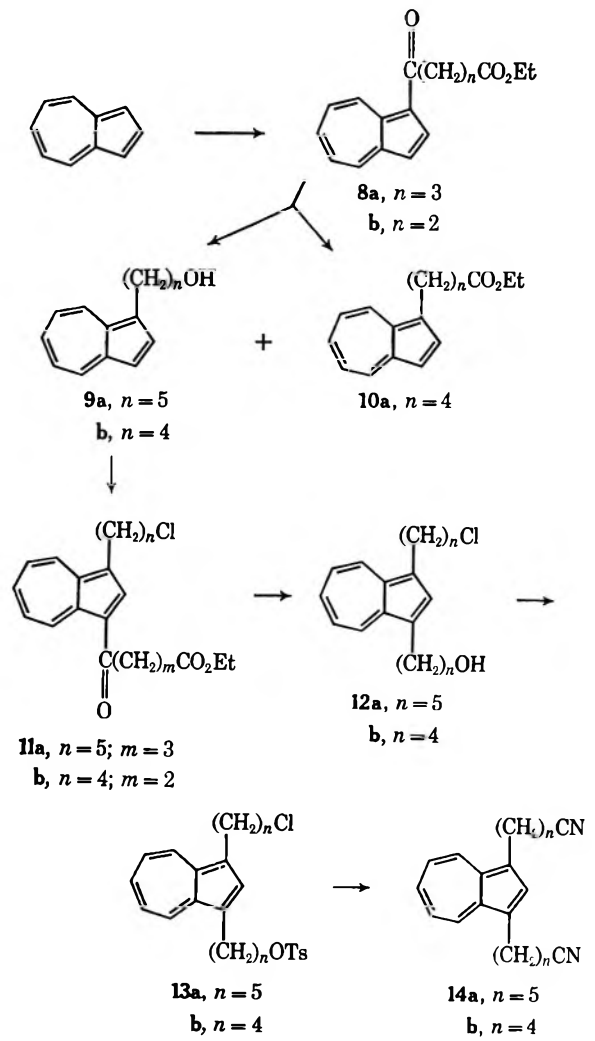
(16) E. J. Cowles, Ph.D. Thesis, University of Washington, 1953, pp 146–149; J. A. Nelson, Ph.D. Thesis, University of Washington, 1950, pp 121–125.

(17) K. Hafner and D. L. Dreyer, unpublished results. Private communication from Dr. Dreyer. Trial Wolff–Kishner, modified Wolff–Kishner [D. J. Cram. M. R. V. Sayhun, and G. R. Knox, *J. Amer. Chem. Soc.*, **84**, 1734 (1962)], and Clemmensen reductions on **15**, **16**, and 1,3-diformylazulene, and nickel desulfurization reactions on the bis ethylthio ketals of **18** and 1,3-diacetylazulene were run in the present investigation. All gave negative results.

(18) K. Hafner, H. Pelster, and J. Schneider, *Ann.*, **650**, 62 (1961).

(19) G. R. Pettit, B. Green, P. Hofer, D. C. Ayres, and P. J. S. Pauwels, *Proc. Chem. Soc.*, 357 (1962); G. R. Pettit and D. M. Piatek, *J. Org. Chem.*, **27**, 2127 (1962).

Scheme II

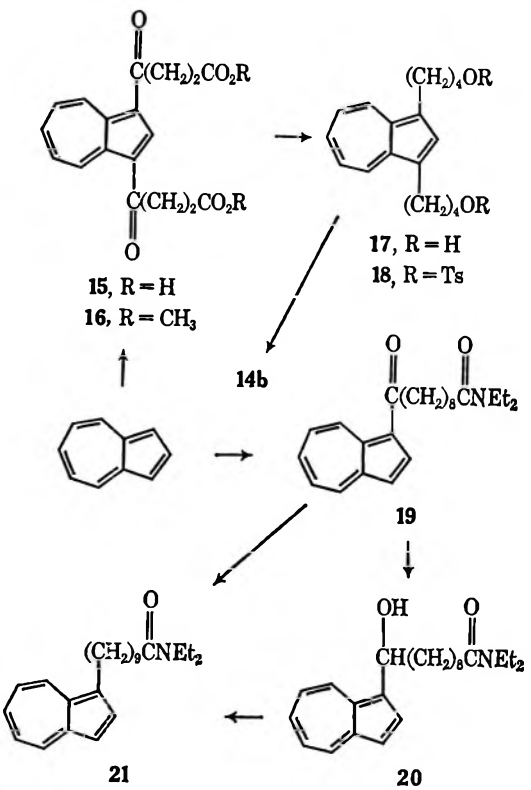


β-propylnaphthalene. A modification of this procedure gave an approximately quantitative reduction of the keto ester (**8a**) to a mixture (*ca.* 9:1) of 5-(1-azulyl)-1-pentanol (**9a**) and ethyl 5-(1-azulyl)pentanoate (**10a**). Under different reaction conditions, a higher yield (52%) of **10a** was obtained. The alcohol (**9a**) was then treated with ethyl N,N-diethylglutaramate under Vilsmeier conditions and a 48% yield of 1-(1′-oxo-4′-carbethoxybutyl)-3-(5′-chloropentyl)azulene (**11a**) resulted. Sodium borohydride–boron trifluoride reduction of **11a**, treatment of the product (presumed to be **12a**) with *p*-toluenesulfonyl chloride, and then reaction of the derivative product (formulated as **13a**) with potassium cyanide in dimethyl sulfoxide gave azulene-1,3-bis(hexanenitrile) (**14a**) in 44% yield from **11a**.

The achievement of this synthesis of **14a** led to the repetition of this scheme using ethyl N,N-diethylsuccinamate in the Vilsmeier steps. In this manner the corresponding compounds **8b** (44%), **11b** (34% from **8b**), and **14b** (36% from **11b**) having one less carbon in the side chains were isolated and characterized.

The success of the Vilsmeier reaction for the preparation of **8** and the fact that Friedel–Crafts acylation conditions which gave disubstitution directly had been readily found[20] led to an attempt to achieve the disubstitution of azulene using an excess of N,N-dimethylacetamide and phosphorus oxychloride. An 87% yield of 1-acetylazulene, but no diacetylazulene, was obtained. Despite this result a second route to azulene-1,3-bis(pentanenitrile) (**14b**) involving diacylation was found (Scheme III). Azulene was treated with an excess of succinic anhydride under Friedel–Crafts conditions. The bis keto acid disubstitution product (**15**) was difficult to purify and clean separation from succinic acid was obtained only after esterification to form the bis keto ester (**16**). Despite the trial of many different reaction conditions, the best yield of **16** obtained was 15%. Curiously, the optimum conditions found for disubstitution resulted in the recovery of more than half of the azulene, but no monosubstitution product was observed.[21] In carrying out the synthesis of **14b** the crude bis keto acid (**15**) was reduced directly to the diol (**17**) by the sodium borohydride–boron trifluoride reagent. The diol was then converted into the tosylate (**18**) and finally to **14b** in the same manner as before.

Scheme III



The Vilsmeier reaction of azulene with N,N,N′,N′-tetraethyldecanediamide (Scheme III) gave the monosubstitution product (**19**) which could not be completely separated from starting materials and so the crude product was reduced with sodium borohydride to N,N-diethyl-10-(1-azulyl)-10-hydroxydecanamide (**20**). Further reduction of **20** by sequential treatment with perchloric acid and sodium borohydride, or the treatment of **19** with sodium borohydride–boron trifluoride gave N,N-diethyl-10-(1-azulyl)decanamide (**21**). The latter method was the better in this case and gave an over-all yield from azulene of 31%. A minor by-product of the several steps was tentatively identified as 1,10-bis(1-azulyl)decane, which could have been formed

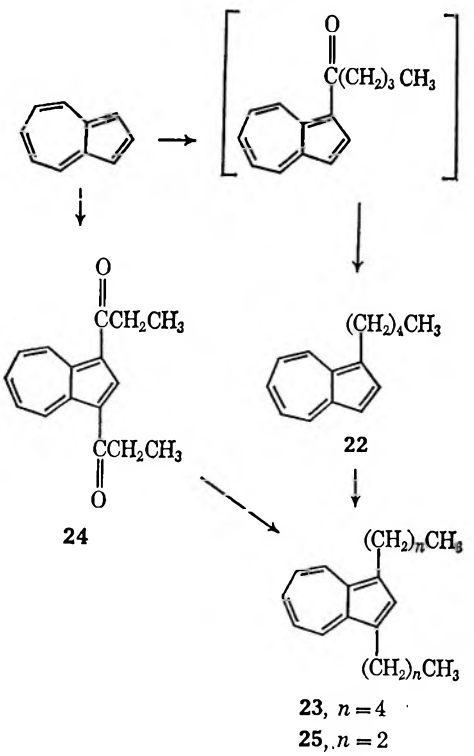
(20) A. G. Anderson, Jr., J. A. Nelson, and J. J. Tazuma, *J. Amer. Chem. Soc.*, **75**, 4980 (1953).

(21) This phenomenon had been observed earlier with the aluminum chloride catalyzed acetylation of azulene.[20]

by further Vilsmeier substitution of azulene by **19** and subsequent reduction.

As no 1,3-polymethylene-substituted azulenes had been characterized previously, it was desirable to have a model compound of this type as a spectral standard. For this purpose 1,3-dipentylazulene (**23**) was synthesized (Scheme IV), again using the Vilsmeier method

SCHEME IV



with N,N-diethylvaleramide as the reagent. The crude ketonic product was subjected to the sodium borohydride–boron trifluoride reduction and 1-pentylazulene (**22**) was obtained in 78% yield. Reduction of the crude keto compound by externally generated diborane gave a somewhat lower yield (59%) of **22**. Repetition of the Vilsmeier acylation and then reduction afforded **23** in 74% yield (55.5% from azulene). Application of the sodium borohydride–boron trifluoride reduction to 1,3-dipropionylazulene (**24**) provided an additional spectral reference compound, 1,3-dipropylazulene (**25**).

A compilation of the principal maxima in the visible spectra of 1-alkyl- and 1,3-dialkylazulenes is given in Table I. If the relatively small deviations are real, it is curious that the *n*-propyl group causes the largest bathochromic shift for the monoalkyl compounds, whereas the methyl group does this for the dialkyl derivatives.

The successful application of the above hydride reductions to azulene species concerned merits further comment. Wechter[22] had found that diborane in tetrahydrofuran reduced xanthone to xanthene but, under similar conditions, benzophenone, *o*-methoxybenzophenone, *p,p'*-dimethoxybenzophenone, and fluorenone were converted only into the alcohols. Also,

(22) W. F. Wechter, *J. Org. Chem.*, **28**, 2935 (1963).

TABLE I

PRINCIPAL VISIBLE MAXIMA OF 1-ALKYL AND 1,3-DIALKYLAZULENES[a]

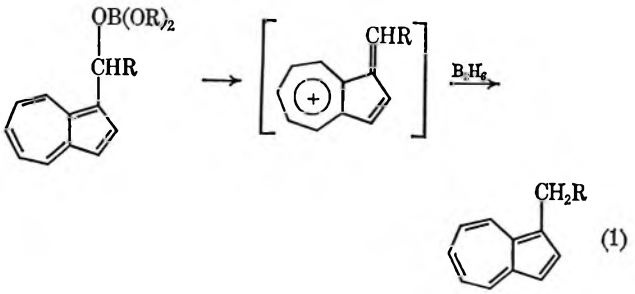
1-Alkyl or 1,3-dialkyl	λ_{max}, mμ	Ref
Methyl	608	*b*
Ethyl	610, 608	*b, c*
n-Propyl	613	*b*
Isopropyl	604, 607	*d, b*
n-Butyl	606	*e*
s-Butyl	610	*b*
t-Butyl	607	*d*
n-Pentyl	608	*c*
Dimethyl	638, 635	*b, f*
Diisopropyl	632	*d*
Di-*n*-propyl	631	*c*
Di-*n*-pentyl	632	c

[a] In solvents of low polarity (*e.g.*, alkanes). [b] E. Heilbronner, "Non-Benzenoid Aromatic Hydrocarbons," D. Ginsberg, Ed., Interscience, New York, N. Y., 1959, p 226. [c] Present work. [d] K. Hafner, H. Pelster, and J. Schneider, *Ann.*, **650**, 62 (1961). [e] R. C. Rhodes, Ph.D. Thesis, University of Washington, 1963, p 40. [f] K. Hafner and W. Senf, *Ann.*, **656**, 34 (1962).

sodium borohydride reduced xanthone to xanthol. Wechter concluded that the reduction of xanthone involved the participation of an unshared electron pair of the ether oxygen. One might, *a priori*, have considered that diborane was therefore not solely responsible for the reduction of β-propionylnaphthalene to β-propylnaphthalene.[19] A further observation of pertinence is that indole-3-aldehydes, ketones, -carboxylic acids, esters, -carbinols, and -carbinyl ethers are readily transformed by lithium aluminum hydride in ether into the corresponding methylene compounds if the indole nitrogen bears a hydrogen,[23] but the N-alkyl analogs are reduced only to the alcohol stage.[24] If aluminum chloride is added, however, 3-acetyl-N-methylindole is reduced by lithium aluminum hydride to 3-ethyl-N-methylindole in 74% yield and this method has been applied with general success[25] for the conversion of the carbonyl in diaryl and arylalkyl ketones into a methylene. It would appear, therefore, that the hydride donors in these reactions can effect the hydrogenolysis step only if a sufficiently stabilized intermediate, as with xanthone and N-hydrogen indoles, or reactive species (aluminum chloride complexed arylcarbinyloxyaluminum species) is involved. The pK_R^+ values for the xanthyl system (−0.84)[26] and for the di-*p*-anisylmethyl system (−5.71),[27] for example, are in agreement with this line of reasoning. No quantitative data on the stability of the 1-azulylmethyl cation are available but studies by Long and Schulze[28] led to approximate pK values of −1.7 and −0.83 for azulene and 1-methylazulene, respectively. These pK values are not strictly comparable with pK_R^+ values but provide a good indication that the 1-azulylmethyl cation has a considerably greater stability than does the di-*p*-anisylmethyl cation, relative to their respective

(23) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).
(24) K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, **28**, 3202 (1963).
(25) R. F. Nystrom and C. R. A. Berger, *J. Amer. Chem. Soc.*, **80**, 2896 (1961); J. Blackwell and W. J. Hickenbottom, *J. Chem. Soc.*, 1405 (1961); B. R. Brown and A. M. S. White, *ibid.*, 3755 (1957).
(26) N. C. Deno and W. L. Evans, *J. Amer. Chem. Soc.*, **79**, 5804 (1957).
(27) N. C. Deno and A. Schriesheim, *ibid.*, **77**, 3051 (1955).
(28) F. A. Long and J. Schulze, *ibid.*, **86**, 327 (1964).

alcohols, and this could account for the reduction of the 1-acylazulenes by diborane (eq 1).

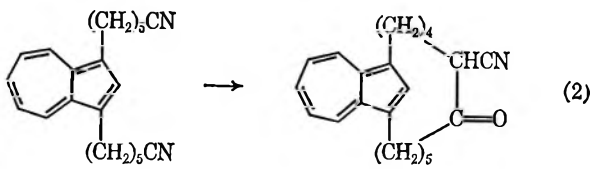


(1)

Diborane is reported to react quite slowly with esters[29] and the use of diborane in the absence of a Lewis acid catalyst would thus be predicted to be the reagent of choice for the selective reduction of keto esters **8**, **11**, and **16** to the saturated esters, whereas sodium borohydride–boron trifluoride reduced both groups readily even at 0°.

Phenol has been reported to react with acrylonitrile in the presence of aluminum chloride to give β-(*p*-hydroxyphenyl)propionitrile in good yield.[30] Attempts to apply this reaction to azulene were not successful.

For the formation of a 1,3-bridged azulene structure the Thorpe–Ziegler ring-closure reaction was run on the dinitriles **14a** and **14b** using a procedure adapted from the work of Allinger, *et al.*[31] From **14a** a 31% yield (5.4% from azulene) of 1,3-(5′-cyano-6′-oxoundecamethylene)azulene (**26**) was obtained (eq 2). The observed maximum of 629 mμ in the visible indicated that the azulene ring was probably not distorted by the 11-carbon bridged ring. Repetition of the Thorpe–Ziegler reaction with **14b**, however, did not give a product which could be identified as the desired bridged structure.



(2)

14a **26**

A high-dilution Vilsmeier procedure was carried out with the azulyldecanamide (**21**) in the hope that some 1,3-cyclized product would be formed, but the small and impure quantities of nonpolymeric materials obtained showed hydroxyl as well as carbonyl absorption and maxima in the region 628–632 mμ, and no product could be identified as the cyclic ketone expected.

Cram, *et al.*, found the acyloin condensation to be the preferred method of ring closure for the preparation of [12]-, [10]-, and [9]paracyclophanes.[32] It was found that azulene reacted with sodium under the conditions of the acyloin reaction to give a dark red-brown solution from which, after 90 min, only 12% of the azulene could be recovered.[33] Therefore a large excess of sodium was to be avoided. A reaction using an ester/sodium mole ratio of 1:4.7 was run with diethyl azulene-1,3-dipropanoate (**6**) but the only azulenic material recovered was the original ester (75%).

An X-ray structural analysis of the azulene-1,3-dipropanoic acid prepared in this work has been carried out by Ammon and Sundaralingam.[34]

Experimental Section

General.—Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Ultraviolet and visible spectra were recorded with either a Model 115 or 14 Cary recording spectrophotometer and, unless otherwise specified, were recorded using the same solvent. Infrared spectra were taken on a Perkin-Elmer Model 21 recording spectrophotometer. A Mechrolab Model 301A osmometer was used to determine molecular weights. Microanalyses were performed by Dr. A. Bernhardt, Microanalytical Laboratory, Max Planck Institute, Mülheim (Ruhr), Germany.

Dimethyl sulfoxide was distilled under vacuum and dried over 4-Å molecular sieves just prior to use. Boron trifluoride etherate was distilled and kept protected from moisture and light. Diglyme was dried over 4-Å molecular sieves. Tetrahydrofuran was distilled from potassium. Nitrogen was passed through sulfuric acid, over Drierite, and finally over hot copper wire.[35] Unless otherwise noted anhydrous sodium sulfate was used to dry solutions of compounds purified by distillation or chromatography. The latter were then concentrated to near dryness on a water bath with a rotary evaporator under aspirator pressure. The petroleum ether had bp 30–60°. Purified solvents were used for the purification and spectra of azulene derivatives. Crystalline compounds were obtained from the final eluent solvent unless otherwise specified. Analytical samples of unstable compounds were handled under nitrogen, and repeated attempts were made to achieve analytical purity for those not so obtained.

Azulyl-1,3-bis(methyltrimethylammonium) Diiodide (1).—This compound was obtained as fine, violet crystals in 98% yield by the treatment of 1,3-bis(dimethylaminomethyl)azulene[4] with an excess of CH_3I in ethanol. The salt decomposed on heating such that no characteristic temperature range could be recorded.[6] An ethanol solution showed λ_{max} (OD_{max}) at 537 (1.06), 567 (0.97, sh), and 624 mμ (0.36, sh) as reported.[36]

1,3-Bis(2′,2′-dicarboxyethyl)azulene (2).—To the solution formed from the reaction of 920 mg (40 mmol) of Na and 100 ml of absolute ethanol was added 8 ml (53 mmol) of distilled diethyl malonate under anhydrous conditions. The mixture was stirred for 10 min and 1.052 g (2 mmol) of **1** was then added in one portion. The solution was heated under reflux for 2 hr, cooled, diluted with 500 ml of water, made slightly acidic with 6 *N* hydrochloric acid, and finally extracted with ether. The residue from the concentration of the ether solution was dissolved in 20 ml of 20% methanolic KOH and the solution was heated under reflux for 105 min. The cooled solution was diluted with 100 ml of water, made slightly acidic with 6 *N* hydrochloric acid, and then continuously extracted with ether for 40 hr. Evaporation of the ether left a solid which was triturated with pentane and dried in a vacuum desiccator. The crude product (3.08 g) contained malonic acid which was removed by sublimation at 125–130° (2 mm). The residue of **2** amounted to 617 mg (86%): mp 171–172°; uv (OD_{max}) (95% ethanol) 236 (0.46), 282 (1.13), 292 (0.82, sh), 349 (0.11), and 367 mμ (0.09); visible (OD_{max}) 615 (0.72), 650 (0.63, sh), and 735 mμ (0.22, sh).

Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.47. Found: C, 59.60; H, 4.88.

Azulyl-1,3-bis(propanoic Acid) (3).—A 100-mg (0.28 mmol) sample of the tetraacid (**2**) was heated in a small glass sublimation

(29) H. C. Brown, "Hydroboration," W. A. Benjamin, Ed., New York, N. Y., 1962, p 249.

(30) H. W. Johnston and F. J. Gross, *J. Org. Chem.*, **22**, 1264 (1957).

(31) N. L. Allinger and S. Greenberg, *J. Amer. Chem. Soc.*, **84**, 2394 (1962); *ibid.*, **81**, 5733 (1959); N. L. Allinger, M. Nakazaki, and V. Zalkow, *ibid.*, **81**, 4074 (1959).

(32) D. J. Cram. N. L. Allinger, and H. Steinberg, *ibid.*, **76**, 6132 (1954); D. J. Cram and H. Daenkier, *ibid.*, **76**, 2743 (1954); D. J. Cram and M. F. Antar, *ibid.*, **80**, 3109 (1958).

(33) The formation of a similar red-brown solution with sodium in tetrahydrofuran from which only *ca.* 8% 1-azuloic ester products could be obtained had also been observed: A. G. Anderson, Jr., D. J. Gale, R. N. McDonald, R. G. Anderson, and R. C. Rhodes, *J. Org. Chem.*, **29**, 1373 (1964).

(34) H. L. Ammon and M. Sundaralingam, *J. Amer. Chem. Soc.*, **88**, 4794 (1966).

(35) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 219.

(36) T. S. Fujita, M. S. Thesis, University of Washington, 1959.

apparatus[37] at 160° (2 mm) for 8 hr giving 36 mg (21%) of **3** as long needles: mp 183–184°; uv (OD_{max}) (95% ethanol) 238 (0.17), 282 (0.64), 349 (0.06), and 367 mμ (0.04); visible (OD_{max}) 618 (0.53), 673 (0.43, sh), and 750 mμ (0.15, sh).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.78; H, 6.05.

1,3-Bis(3′-oxobutyl)azulene (5).—To the solution formed from 460 mg (20 mg-atoms) of Na and 40 ml of absolute ethanol was added 4 ml (30 mmol) of distilled ethyl acetoacetate under anhydrous conditions. The mixture was stirred for 10 min and 526 mg (1 mmol) of the bis quaternary salt (**1**) was added in one portion. The solution was heated under reflux for 2 hr, cooled to room temperature, diluted with 200 ml of water, and then extracted with ether. The extract was washed twice with water and once with saturated NaCl solution. The product from the concentration of the dried (Na_2SO_4) solution was dissolved in 30 ml of 10% methanolic KOH and the solution was heated under reflux for 1 hr. The heating bath was removed and 7 ml of 12 *N* sulfuric acid was added carefully to the hot, stirred solution. Carbon dioxide evolution ceased after *ca.* 10 min. and the solution was cooled (ice bath), diluted with 200 ml of water, and extracted with ether. The extract was washed with water and NaCl solution, and then dried. Chromatography over acidic alumina (CH_2Cl_2) gave 216 mg of blue solid which afforded 143 mg (53%) of **5** after recrystallization from cyclohexane: mp 64–66°; ir (CCl_4) 5.80 μ (carbonyl); uv (OD_{max}) (cyclohexane) 233 (0.78), 282 (1.37), 350 (0.12), and 3.68 mμ (0.10); visible (ε) 625 (331), 683 (271), and 760 mμ (89).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.55; H, 7.45.

1,3-Bis(2′-carbethoxy-3′-oxobutyl)azulene (4).—A solution of ethyl sodioacetoacetate was prepared in the manner described from 920 mg (40 mg-atoms) of Na, 100 ml of absolute ethanol, and 8 ml (61 mmol) of ethyl acetoacetate and to this was added 1.052 g (2 mmol) of the bis quaternary salt (**1**). The solution was heated under reflux for 2 hr and then allowed to stand at room temperature for 7 hr before dilution with 700 ml of water and then extraction with ether until the aqueous layer was colorless. The material from the concentration of the dried extract was heated at 50° (0.5 mm) for 4 hr and then chromatographed over acidic alumina. Elution with CH_2Cl_2 gave 660 mg (80%) of **4** as a blue oil: ir (CCl_4) 5.75, 5.80 μ; uv (log ε) (ethanol) 234 (4.00), 282 (4.61), 285 (4.58, sh), 348 (3.65), and 365 mμ (3.57); visible (ε) 610 (293), 650 (246), and 830 mμ (87).

Anal. Calcd for $C_{24}H_{28}O_5$: C, 69.88; H, 6.84. Found: C, 70.01; H, 6.86.

Diethyl Azulene-1,3-dipropanoate (6).—To 20 ml of absolute ethanol in a dry flask equipped with a 20-cm column packed with metal helices was added 5 mg (0.2 mg-atom) of Na. When the Na had reacted, 308 mg (0.75 mmol) of the above diacetoacetate compound (**5**) in 5 ml of absolute ethanol was added and the mixture was heated to reflux. The temperature at the top of the column rose to 78°, dropped to 77° after 3.5 hr, and remained there for 12 hr. Distillation of the solvent was begun and after 45 min 10 ml of distillate had been collected and the vapor temperature was 79°. Distillation was stopped and reflux continued with the vapor temperature at 79° for 5 hr. An odor of ethyl acetate was noted from the distillate. The cooled reaction mixture was diluted with 200 ml of water and extracted with ether until the aqueous layer was colorless. The washed (water) extract was dried and the concentrate from this was chromatographed over acidic alumina. Elution with 7:3 petroleum ether–methylene chloride gave 170 mg (69%) of **6** as a blue oil: ir (CCl_4) 5.75 μ; uv (log ε) (ethanol) 244 (3.98), 282 (4.63), 350 (3.66), and 367 mμ (2.56); visible (ε) 618 (280), 670 (230), and 745 mμ (75).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.59; H, 7.90.

1,3-Bis(3′-hydroxypropyl)azulene (7).—A solution of 122 mg (0.37 mmol) of the above diester (**6**) in 5 ml of ether (distilled from NaH) was added over 5 min to 76 mg (2 mmol) of $LiAlH_4$ and 10 ml of the dry ether stirred under nitrogen at 0° and the mixture was then stirred for 1 hr. The excess hydride was destroyed by the addition of 5 ml of water and the mixture was then poured into 0.5 ml of cold 10% sulfuric acid, vigorously shaken until the complex had decomposed, and then extracted with ether. The washed (20 ml of 5% $NaHCO_3$), dried, concentrated organic fraction was chromatographed over silica gel (ether) giving 82 mg (91%) of **7** as a blue oil: ir ($HCCl_3$) 2.71 and 2.89 μ.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 77.91; H, 8.31.

Ethyl N,N-Diethylglutaramate.—To a solution of 17.1 g (0.15 mol) of glutaric anhydride[38] in 30 ml of benzene was added 34 ml (0.32 mol) of diethylamine over a 10-min period and the mixture was then heated under reflux for 1 hr. After removal of most of the solvent, a solution of 15 ml of absolute ethanol, 30 ml of benzene, and 2 ml of concentrated sulfuric acid was added and the reaction mixture was then heated under reflux overnight using a Dean–Stark trap. The cooled solution was diluted with 100 ml of water and extracted with ether, and the ether extract was washed with water and then with saturated NaCl solution. Distillation of the dried solution yielded a forerun, bp 81–83° (1.5 mm), of about 2 g which was discarded. The product was collected at bp 121–123° (1.5 mm) [lit.[15] bp 115–118° (0.5 mm) and weighed 16.8 g (52%).

Ethyl 5-(1-Azulyl)-5-oxopentanoate (8a).—To a stirred solution of 560 mg (4.38 mmol) of azulene and 2 ml (9.3 mmol) of ethyl N,N-diethylglutaramate in 5 ml of dry tetrahydrofuran at 0° was added 2 ml (15.5 mmol) of $POCl_3$ under anhydrous conditions. The mixture was stirred for 15 min at 0° and for 30 min at room temperature and finally was heated under reflux for 6 hr. The cooled solution was diluted with 100 ml of water, made slightly basic with 10% KOH, and then extracted with ether. The extract was washed twice with 50 ml of saturated NaCl, dried, concentrated, and chromatographed over acidic alumina. Elution with 9:1 petroleum ether–methylene chloride afforded 50 mg of azulene, and then 4:1 petroleum ether–methylene chloride removed a yellow oil, which was discarded, followed by 1.029 g (86%, 95% net) of keto ester **8a**, mp 38–41°. Two additional chromatographic purifications provided the analytical sample as a maroon solid: mp 45–46°; ir (CCl_4) 5.75 and 6.05 μ; uv (OD_{max}) (cyclohexane) 230 (0.56), 283 (0.59), 305 (0.69), 368 (0.12), and 382 mμ (0.13); visible (OD_{max}) 530 (0.67, sh), 548 (0.77), 565 (0.68, sh), 593 (0.65), and 652 mμ (0.25). The corresponding methyl ester and acid have been reported.[7b]

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.64; H, 6.80.

1-Acetylazulene.[39]—Under anhydrous conditions 3 ml (22.5 mmol) of $POCl_3$ was added dropwise to a stirred solution of 630 mg (5 mmol) of azulene in 5 ml of dry (molecular sieves) N,N-dimethylacetamide. The mixture was stirred for 5 min at room temperature and at 80° for 2 hr, then cooled, and diluted with 100 ml of water. The red solution was made slightly alkaline with 10% KOH and extracted with ether. The extracts were washed with five 50-ml portions of water and once with saturated NaCl solution, dried, concentrated, and chromatographed over acidic alumina. Petroleum ether–methylene chloride (9:1) eluted a trace of azulene and petroleum ether–methylene chloride (3:1) removed 737 mg (87%) of 1-acetylazulene having the spectra reported.[20]

1-Ethylazulene. Method A.—To a solution of 141 mg (0.83 mmol) of 1-acetylazulene in 5 ml of 95% ethanol containing 5 drops of 10% KOH was added 200 mg (5.1 mmol) of $NaBH_4$ and the reaction mixture was stirred for 5.5 hr at room temperature. Ice water (50 ml) was added, the mixture was extracted with ether, and the extract was washed three times with water and once with saturated NaCl solution. The concentrate from the dried solution was chromatographed over basic alumina and elution with 1:1 methylene chloride–ether afforded a blue oil (*ca.* 74 mg, 52%) presumed to be 1-(α-hydroxyethyl)azulene: uv (OD_{max}) (CH_2Cl_2) 240 (0.32), 279 (0.99), 285 (0.90), 34 (0.09), and 359 mμ (0.06); visible (OD_{max}) 590 (1.22), 625 (1.10, sh), and 700 mμ (0.42, sh); ir 2.79 and 2.91 μ. This product was quite unstable, as reported,[13] and was used immediately in the next step.

A flask with a sintered-glass bottom attached to a filter bell was equipped with a pressure-equalized dropping funnel and a stirrer. It was dried, flushed with nitrogen, and cooled to 0° before 10 ml of anhydrous ether, 1 ml of acetic anhydride, and then 0.3 ml of 70% perchloric acid were introduced. The solution was stirred for 5 min at 0°, the ice bath was replaced by one containing Dry Ice–methanol, and the above blue oil was dis-

(37) Reference 35, p 115.

(38) We are grateful to the Textile Fibers Department, E. I. du Pont de Nemours and Co., for a generous sample of this compound.

(39) This procedure is a modification of the method of Hafner and Bernhard[13] which gave a 70% yield.

solved in 10 ml of methylene chloride–ether (1:1) and added over a period of 10 min. The solvent was removed (filtration) and the precipitate was washed with two 10-ml portions of dry ether. The temperature was increased to 0° and 5 ml of CH_3NO_2 (dried over acidic alumina) was added. To the stirred yellow-brown solution was added 100 mg (2.5 mmol) of $NaBH_4$, which turned the solution blue. After 15 min the contents of the flask were removed, taken up in ether, and washed three times with water. The concentrate from the dried organic fraction was chromatographed over basic alumina. Petroleum ether–methylene chloride (5:1) eluted 35 mg (27%) of 1-ethylazulene as a blue oil: uv (OD_{max}) (cyclohexane) 238 (0.63), 280 (1.48), 345 (0.14), and 362 mμ (0.10); visible (OD_{max}) 584 (1.37). 608 (1.62), 633 (1.56), 665 (1.43), 698 (0.90), 738 (0.525), and 773 mμ (0.14) in agreement with the reported spectra.[40] The ir spectrum showed no absorption for hydroxyl or carbonyl functions.

Method B.—To a solution of 15 mg (0.09 mmol) of 1-acetylazulene in 0.5 ml of anhydrous ether was added 0.5 ml (4 mmol) of boron trifluoride etherate. The orange solution was added over 30 min to 100 mg (2.6 mmol) of $NaBH_4$ in 1 ml of diglyme at 0° with stirring. The mixture was stirred 1 hr longer, poured into 50 ml of ice water, and extracted with petroleum ether. Chromatography (basic alumina and petroleum ether) of the concentrate from the washed (water), dried extract gave 9 mg (64%) of 1-ethylazulene identical (ir, uv, and visible spectra) with the product from method A.

Ethyl 5-(1-Azulyl)pentanoate (10a).—To a solution of 135 mg (0.5 mmol) of the above keto ester (8a) and 100 mg (2.6 mmol) of $NaBH_4$ in 2 ml of dry diglyme stirred at 0° was added 0.5 ml (4 mmol) of boron trifluoride etherate over a period of 10 sec. The mixture was stirred for 3 min and then poured into 50 ml of ice water. The aqueous product was extracted with ether and the concentrate from the washed (water and saturated NaCl) and dried extract was chromatographed over basic alumina. Elution with 1:1 petroleum ether–methylene chloride gave 68 mg (52%) of **10a** as a blue oil: ir (CCl_4) 5.75 μ; uv (OD_{max}) (cyclohexane) 238 (0.31), 275 (0.81), 279(0.82), 285 (0.85), 345 (0.09), and 362 mμ (0.06); visible (OD_{max}) 562 (0.56 sh), 582 (0.66), 606 (0.80), 632 (0.68), 663 (0.70), 698 (0.32, sh), and 736 mμ (0.29).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.43; H, 8.03.

1-(1′-Oxo-4′-carbethoxybutyl)-3-(5′-chloropentyl)azulene (11a).—To a solution of 270 mg (1 mmol) of the above keto ester (8a) in 2 ml of anhydrous ether was added 1.5 ml (12 mmol) of boron trifluoride etherate. The mixture was added under anhydrous conditions to a stirred solution of 500 mg (12.8 mmol) of NaH in 5 ml of diglyme at 0° over a period of 30 min. Stirring was continued for 30 min and the mixture was then poured into 50 ml of ice water and extracted with ether. The concentrate from the washed (twice with saturated NaCl solution) and dried extract was chromatographed over basic alumina. Elution with 1:1 petroleum ether–methylene chloride afforded 19 mg (7%) of **10a**, and ether then eluted 215 mg (*ca.* 100%) of blue oil: ir (neat) 2.9 μ (OH); uv (OD_{max}) (cyclohexane) 233 (0.60), 279 (1.02), 346 (0.10) and 362 mμ (0.07); visible (OD_{max}) 562 (0.68, sh), 585 (0.80), 607, (0.98), 633 (0.84), 666 (0.86), 700 (0.38 sh), and 738 mμ (0.35). The spectra indicated that the product was primarily 5-(1-azulyl)-1-pentanol (9a).

The blue oil (215 mg) and 0.5 ml (2.3 mmol) of ethyl N,N-diethylglutaramate were dissolved in 2 ml of dry tetrahydrofuran. To the cooled (0°), stirred solution was added, dropwise, 0.5 ml (3.9 mmol) of $POCl_3$ under anhydrous conditions. The mixture was stirred for 10 min at 0°, 30 min at room temperature, and 2 hr under reflux, then was cooled, diluted with 100 ml of water, made slightly basic with 10% KOH, and extracted with ether. The concentrate from the washed (twice with water and once with saturated NaCl) and dried extract was chromatographed over acidic alumina. Elution with 2:1 methylene chloride–petroleum ether removed a pale yellow-green oil (which was discarded) followed by 181 mg (48% from **8a**) of **11a** as an oil which crystallized as green needles, mp 40–42°. Rechromatography gave the analytical sample: mp 42–43°; ir (CCl_4) 5.75 and 6.07 μ; uv (OD_{max}) (cyclohexane) 231 (0.35), 265 (0.14, sh), 298 (0.36), 309 (0.43), 378 (0.08), and 397 mμ (0.08); visible (OD_{max}) 572 (0.84), 620 (0.66), and 688 mμ (0.22).

Anal. Calcd for $C_{22}H_{27}O_3Cl$: C, 70.49; H, 7.21; Cl, 9.48. Found: C, 70.63; H, 7.09; Cl, 9.29.

Azulene-1,3-bis(hexanenitrile) (14a).—To a solution of 187 mg (0.5 mmol) of the above chloro keto ester (**11a**) in 1.5 ml of ether was added 1 ml (8 mmol) of boron trifluoride etherate. This red solution was added dropwise to a stirred solution of 250 mg (6.4 mmol) of $NaBH_4$ in 2 ml of diglyme at 0° over a period of 30 min and the mixture was stirred an additional 30 min before it was added to 100 ml of ice water. The aqueous mixture was extracted with ether and the extract was washed with saturated NaCl and then dried. The concentrate was chromatographed over basic alumina. Petroleum ether–methylene chloride (1:1) eluted 10 mg of unchanged **11a** and then methylene chloride–ether (1:1) gave 153 mg (96%) of a blue oil presumed to be 1-(5′-chloropentyl)-3-(5′-hydroxypentyl)azulene (**12a**): ir (neat) 2.95 μ; uv (OD_{max}) (cyclohexane) 240 (0.28), 283 (1.03), 351 (0.12), and 368 mμ (0.10); visible (OD_{max}) 630 (1.13), 661 (0.41), and 774 mμ (0.34).

To a solution of 347 mg (1.19 mmol) of the blue oil in 5 ml of dry (KOH) pyridine stirred at 5–10° was added 573 mg (3 mmol) of *p*-toluenesulfonyl chloride over a 10-min period. The mixture was stirred at 18° for 3 hr, about 10 g of ice and 10 ml of 3 *N* hydrochloric acid was then added, and the whole was extracted with ether. The extract was washed twice with water and once with saturated NaCl and dried. The concentrate was chromatographed over basic alumina and 1:1 petroleum ether–methylene chloride eluted 359 mg (64%) of a blue oil presumed to be *p*-toluenesulfonate ester (**13a**) of the alcohol (**12a**): ir (neat) 6.25, 7.38, 8.43 and 8.51 μ (characteristic of tosylates) and no hydroxyl absorption. The visible spectrum (cyclohexane) was essentially identical with that of the immediate precursor alcohol.

A solution of 359 mg (0.76 mmol) of the preceding blue oil in 5 ml of dimethyl sulfoxide was added dropwise to a solution of 98 mg (2 mmol) of dry NaCN in 3 ml of dimethyl sulfoxide. The mixture was stirred for 5 min at 25°, heated at 80° for 30 min, cooled, diluted with 100 ml of water, and then extracted with ether. The extract was washed twice with water and once with saturated NaCl and dried. The concentrate was chromatographed over basic alumina. Elution with 2:1 petroleum ether–methylene chloride removed a trace of a blue oil, then 163 mg of a second blue oil was eluted with a 1:1 solution of the same solvents, and 47 mg of a third blue oil was eluted with CH_2Cl_2. The ir spectra (neat) of the two major fractions were very similar except that the absorption for nitrile was more intense in the latter. The former was therefore presumed to be the monochloromononitrile product and was subjected to a second identical treatment with sodium cyanide and work-up procedure. Rechromatography of the product from this, combined with the 47 mg from the initial reaction, over acidic alumina with CH_2Cl_2 as the eluent gave 175 mg (72%) of **14a** as a blue oil: ir (neat) 4.47 μ (CN); uv (OD_{max}) (cyclohexane) 230 (0.74), 282 (1.25), 350 (0.13), and 368 mμ (0.11); visible (OD_{max}) 580 (0.56, sh), 605 (0.67, sh), 628 (0.80), 660 (0.66), 688 (0.67), 730 (0.26, sh), and 767 mμ (0.22).

Anal. Calcd for $C_{22}H_{26}N_2$: C, 83.02; H, 8.18. Found: C, 83.05; H, 8.15.

Ethyl 4-(1-Azulyl)-4-oxobutanoate (8b).—To a cooled (0°) solution of 2.2 ml (11 mmol) of ethyl N,N-diethylsuccinamate, bp 114–115° (1.7 mm) [lit.[15] bp 102–104°, (0.8 mm)], prepared as described by Avison,[16] and 1.28 g (10 mmol) of azulene in 15 ml of dry tetrahydrofuran was added 1 ml (11 mmol) of $POCl_3$ over a period of 2 min. The mixture was stirred at 0° for 5 min and at room temperature for 15 min and was then heated under reflux for 3.5 hr. The cooled solution was diluted with 100 ml of saturated NaCl, made almost neutral (slightly acidic) with 10% KOH, and extracted with CH_2Cl_2. The extract was washed with saturated sodium chloride and dried. Chromatography of the concentrate over acidic alumina and elution with petroleum ether afforded 300 mg of azulene. Elution with 9:1 petroleum ether–diethyl ether removed a yellow oil (discarded) and then 1.131 g (44%, 60% net) of **8b** as a maroon oil: ir (neat) 5.75 and 6.09 μ; uv (OD_{max}) (cyclohexane) 229 (0.98, sh), 260 (0.39, sh), 288 (0.70, sh), 292 (0.80), 298 (0.75, sh), 304 (0.91), 367 (0.16), and 382 mμ (0.18); visible (OD_{max}) 547 (0.70), 565 (0.61, sh), and 591 mμ (0.60). The corresponding methyl ester and acid have been reported.[7b]

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.99; H, 6.43.

(40) Table I, ref *b*.

1-(4′-Chlorobutyl)-3-(1′-oxo-3′-carbethoxypropyl)azulene (11b).—To a solution of 964 mg (3.76 mmol) of the above keto ester (**8b**) in 5 ml of dry ether was added 1.5 ml (12 mmol) of boron trifluoride etherate. The resulting red solution was added, under anhydrous conditions, over a 25-min period to 500 mg (13 mmol) of $NaBH_4$ in 5 ml of diglyme stirred at 0° and the mixture was stirred at 0° for an additional 30 min. The reaction mixture was then poured into 50 ml of cold (0°) 5% KOH and the whole was extracted with ether. The extract was washed twice with water and once with saturated NaCl and dried. On chromatography of the concentrate over basic alumina, 1:1 methylene chloride–petroleum ether eluted a trace of blue-green oil (discarded) and 4:1 methylene chloride–ether gave 381 mg (51%) of blue oil presumed to be 4-(1-azulyl)butanol (**9b**): ir (CCl_4) 3.00 μ; uv (OD_{max}) (cyclohexane) 242 (0.43), 278 (1.81), 283 (1.63), 298 (0.16), 346 (0.17), and 362 mμ (0.11); visible (OD_{max}) 560 (0.79, sh), 582 (0.94), 605 (1.15), 631 (0.98), 663 (1.01), 695 (0.45), and 734 mμ (0.41). An unidentified blue oil (136 mg) was finally eluted with 9:1 ether–methanol.

To a stirred solution of 317 mg (1.59 mmol) of the blue oil designated as **9b** and 0.5 ml (2.5 mmol) of ethyl N,N-diethylsuccinamate[15] in 1 ml of dry tetrahydrofuran was added 0.2 ml (2.1 mmol) of $POCl_3$ at 0° under anhydrous conditions. The mixture was stirred at 0° for 10 min, at room temperature for 20 min, and at 80° for 1 hr before being cooled, diluted with 100 ml of water, and made slightly basic with 10% KOH. The whole was extracted with CH_2Cl_2 and the extract was washed twice with saturated NaCl and dried. Chromatography of the concentrate over acidic alumina and elution with 9:1 petroleum ether–methylene chloride removed a blue oil (28 mg). A 2:1methylene chloride–petroleum ether solution then eluted a yellow-green oil (discarded) followed by 368 mg (67%) of **11b** as a violet oil: ir (neat) 5.75 and 6.08 μ; uv (OD_{max}) (cyclohexane) 235 (0.39), 296 (0.53), and 309 mμ (0.65); visible (OD_{max}) 570 (0.56), 618 (0.45), and 682 mμ (0.15).

Anal. Calcd for $C_{20}H_{23}ClO_3$: C, 69.26; H, 6.64. Found: C, 69.85; H, 6.54.

Azulene-1,3-bis(pentanenitrile) (14b). Method A.—To a solution of 263 mg (0.76 mmol) of the above chloro keto ester (**11b**) in 2 ml of anhydrous ether was added 1 ml (8 mmol) of boron trifluoride etherate. The resulting solution was added over a 30-min period under anhydrous conditions to a stirred solution of 150 mg (4 mmol) of $NaBH_4$ in 2 ml of diglyme at 0°. The mixture was stirred an additional 30 min, poured into 50 ml of cold 5% KOH, and extracted with ether. The extract was washed twice with water and once with saturated NaCl and then dried. Chromatography of the concentrate over basic alumina and elution with 1:1 petroleum ether–methylene chloride removed a blue oil (28 mg) and then elution with 9:1 methylene chloride–ether gave 158 mg (76%) of a blue oil presumed to be 1-(4′-chlorobutyl)-3-(4′-hydroxybutyl)azulene (**12b**): ir (neat) 2.96 μ; uv (OD_{max}) (cyclohexane) 233 (0.55), 282 (1.12), 350 (0.12), and 368 mμ (0.11); visible (OD_{max}) 608 (0.64), 629 (0.75), 659 (0.63), 691 (0.63), 725 (0.28, sh), and 770 mμ (0.23).

To a solution of 158 mg (0.57 mmol) of the product designated as **12b** in 5 ml of dry pyridine stirred at 0° was added 345 mg (1.8 mmol) of *p*-toluenesulfonyl chloride over a 10-min period and the mixture was stirred at 15° for 4.5 hr. About 10 g of ice and 10 ml of 2 *N* hydrochloric acid were added and the whole was extracted with ether. The extract was washed three times with cold water and once with saturated NaCl and then dried. The concentrate was chromatographed over basic alumina. A blue oil, 148 mg (58%) presumed to be the *p*-toluenesulfonate derivative (**13b**) of **12b**, was eluted with 1:1 methylene chloride–petroleum ether: ir (neat) 6.25, 7.36, 8.43, and 8.53 μ (tosylate) and no absorption for hydroxyl. The uv and visible spectra (cyclohexane) were very similar to those of **12b**.

A solution of 145 mg (0.33 mmol) of the product designated as **13b** in 5 ml of dry dimethyl sulfoxide was added under anhydrous conditions to 98 mg (2 mmol) of dry NaCN in 1 ml of dimethyl sulfoxide. The stirred mixture was heated at 80° for 30 min, then cooled, and diluted with 50 ml of water, and the whole was extracted with ether. The extract was washed several times with water and once with saturated NaCl and dried. Chromatography of the concentrate over basic alumina and development with 1:1 methylene chloride–petroleum ether gave two blue bands. The product (31 mg) from the first was assumed to be monochloride–mononitrile and was subjected to reaction with 98 mg (2 mmol) of NaCN in 5 ml of dimethyl sulfoxide as just described and the product was combined with the second fraction from the initial chromatograph. Rechromatography of the combined material with the same eluent gave a trace of blue oil as the first fraction and the main product (**14b**), 79 mg (82%), was removed with 2:1 methylene chloride–petroleum ether and obtained as a blue oil: ir (neat) 4.45 μ (CN); uv (log ε) (ethanol) 231 (4.47), 282 (4.74), 349 (3.70), and 366 mμ (3.58); visible (ε) 625 (313), 682 (258), and 765 mμ (88).

Anal. Calcd for $C_{20}H_{22}N_2$: C, 82.76; H, 7.59. Found: C, 82.47; H, 7.86.

Method B.—Under anhydrous conditions a mixture of 2.2 g (22 mmol) of powdered succinic anhydride, 5.36 g (40 mmol) of anhydrous $AlCl_3$, and 100 ml of CH_2Cl_2 was warmed at 35° for 10 min with stirring. The mixture was cooled to 0° and, with stirring and purging with nitrogen, a solution of 1.28 g (10 mmol) of azulene in 50 ml of CH_2Cl_2 was added over a period of 20 min. Azulene remaining in the funnel was rinsed into the flask with 25 ml of CH_2Cl_2 and the total mixture was stirred at 15° for 3 hr and then poured into 50 ml of 2 *N* hydrochloric acid at 0°. The resulting red precipitate was collected by filtration and washed with cold CH_2Cl_2. The organic fraction of the filtrate was extracted three times with 10% Na_2CO_3 (extracts saved) and once with saturated NaCl and dried. Chromatography of the concentrate over acidic alumina and elution with petroleum ether afforded 640 mg (5 mmol) of azulene. The combined extracts were acidified with 6 *N* hydrochloric acid and the collected red precipitate was added to that obtained earlier. The combined product was rinsed with water and dried *in vacuo* over Drierite. This product was presumed to be mostly the bis keto acid (**15**) and appeared to be contaminated with succinic acid.

In a separate run, esterification of a methanol solution of this material with excess ethereal CH_2N_2 in the usual manner and purification by chromatography over acidic alumina (elution with 1:20 ether–methylene chloride to remove small yellow and red fractions and then with ether) gave a 15% (58% net) yield (0.537 g from 1.28 g of azulene) of 1,3-bis(1′-oxo-3′-carbomethoxypropyl)azulene (**16**) which crystallized from acetone as red needles: mp 108–109°; ir (KBr pellet) 5.79 and 6.06 μ; uv (OD_{max}) (ethanol) 305 (1.47), 375 (0.69), and 385 mμ (0.67); visible 500 mμ.

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.72; H, 5.91.

The product designated as crude **15** was dissolved in 7 ml of diglyme and to this solution was added 3 ml (24 mmol) of boron trifluoride etherate. The resulting solution, in turn, was added over a 30-min period under anhydrous conditions to 500 mg (13 mmol) of $NaBH_4$ in 5 ml of diglyme stirred at 0°, and then a second equal portion of $NaBH_4$ was added in the same manner. The mixture was stirred an additional 30 min and then poured into 50 ml of cold 5% KOH. After extraction with ether (an emulsion formed which was broken by centrifugation), the extract was washed twice with water and once with saturated NaCl and dried over Na_2SO_4. The solvent was removed and the residue, presumed to be **17**, was taken up in 10 ml of dry pyridine. To the cold (0°) solution was added, with stirring, 3 g (15.8 mmol) of *p*-toluenesulfonyl chloride over a period of 1 hr. After the mixture was stirred 2 hr at 15°, about 10 g of ice and 20 ml of 3 *N* hydrochloric acid were added and the whole was extracted with ether. The extract was washed twice with water and once with saturated NaCl and dried. Chromatography of the concentrate over basic alumina and elution with 2:1 methylene chloride–petroleum ether gave 561 mg of blue oil presumed to be crude ditosylate (**18**): ir (neat) 6.25, 7.36, 8.43, and 8.53 μ (tosylate) along with a weak band at 5.75 μ; visible (cyclohexane–carbon tetrachloride) 629 mμ.

A solution of the blue product in 5 ml of dimethyl sulfoxide was added to 196 mg (4 mmol) of dry NaCN in 1 ml of dimethyl sulfoxide. The mixture was stirred for 5 min at room temperature and for 10 min at 80°. It was allowed to cool and diluted with 100 ml of water, and the whole was extracted with ether. The extract was washed three times with water and once with saturated NaCl and dried. Chromatography of the concentrate over basic alumina and elution with 2:1 methylene chloride–petroleum ether yielded 210 mg of blue oil which exhibited absorption at 4.48 (CN) and also at 5.75 μ (tosylate). Rechromatography over acidic alumina with 1:1 methylene chloride–petroleum ether eluent and fractional collection of the eluate effected the separation of the tosylate impurities (in the first fractions) from 116 mg (4%, 8% net from azulene) of **14b** identical (ir spectrum) with the product from method A.

N,N-Diethyl-10-(1-azulyl)decanamide (21). Method A.—To 24 g (0.1 mol) of decanedioyl chloride, mp −6 to −5°, bp 150° (3–4 mm) [lit.[41] bp 109–110° (1 mm)], in 50 ml of dry ether was added a solution of 50 ml (0.48 mol) of diethylamine in 50 ml of dry ether. The mixture was stirred for 3 hr and diluted with 100 ml of water, and the whole was extracted with ether. The extract was washed with 10% KOH, water, and saturated NaCl and then dried. Distillation gave 29.5 g (94%) of pale yellow oil presumed to be the tetraethyldiamide, bp 215–216° (1 mm).

Under anhydrous conditions a solution of 384 mg (3 mmol) of azulene in 1.67 g (5.4 mmol) of the diamide product was cooled to 0° and 0.28 ml (3 mmol) of $POCl_3$ was added with stirring over a 5-min period. The mixture was stirred at room temperature for 10 min and at 80° for 3 hr, cooled, and diluted with 100 ml of water. The solution was made slightly basic with 10% KOH and then extracted with ether. The concentrate from the washed (twice with water and once with saturated NaCl) and dried extract was chromatographed over acidic alumina. Petroleum ether–methylene chloride (4:1) eluted 19 mg of azulene and 1:1 petroleum ether–methylene chloride then removed 1.57 g of a maroon oil. The absorption spectra of this material indicated the presence of both the keto amide (19) and the tetraethyldecanediamide and rechromatography did not effect a separation. The material was dissolved in 10 ml of ethanol and to this solution was added 5 drops of 10% KOH and 500 mg (12.8 mmol) of $NaBH_4$. The mixture was stirred for 3 hr, then diluted with 100 ml of water, and extracted with ether. The concentrate from the washed (twice with water and once with saturated NaCl) and dried extract was chromatographed over basic alumina. A pale yellow-green oil was eluted with 1:1 petroleum ether–methylene chloride and then 1:1 methylene chloride–ether removed 756 mg (69%) of blue oil thought to be N,N-diethyl-10-(1-azulyl)-10-hydroxydecanamide (**20**): ir (neat) 2.90 and 6.10 μ; uv (OD_{max}) (ethanol) 240 (0.54), 278 (1.84), 282 (1.67), 330 (0.15, sh), 342 (0.19), and 358 mμ (0.09); visible (OD_{max}) 590 (0.56), 635 (0.47, sh), and 700 mμ (0.17 sh).

To 20 ml of dry ether and 3 ml of acetic anhydride under a nitrogen atmosphere at 0° in the apparatus described above for the preparation of 1-ethylazulene (method A) was added 1 ml of 70% perchloric acid. The solution was stirred for 30 min and then cooled in a Dry Ice–methanol bath, and 756 mg (2.07 mmol) of the above blue oil (**20**) dissolved in 10 ml of ether was added over a 15-min period. After the mixture stirred for an additional 30 min, the solvent was removed and the brown precipitate was washed with ether. The temperature was increased to 0° and 5 ml of dry CH_3NO_2 was added to give a brown solution which turned blue upon the addition of 500 mg (12.8 mmol) of $NaBH_4$. The solution was stirred for 15 min, diluted with ether, and then washed with water three times. The concentrate from the dried ethereal fraction was chromatographed over acidic alumina and elution with CH_2Cl_2 afforded 115 mg (16% from **20**, 11% from azulene) of **21** as a blue oil: ir (neat) 6.10 μ; uv (OD_{max}) (cyclohexane) 232 (0.48), 274 (0.77), 279 (0.85), 284 (0.79), 347 (0.08), and 362 mμ (0.06); visible (OD_{max}) 584 (1.16), 607 (1.40), 636 (1.23), 665 (1.24), 700 (0.61), and 739 mμ (0.50).

Anal. Calcd for $C_{24}H_{35}NO$: C, 81.59; H, 9.91; N, 3.97. Found: C, 81.61; H, 9.89; N, 3.81.

Ether–methylene chloride (1:1) eluted 285 mg of an unstable blue oil: ir (neat) 2.91 (small) and 6.10 μ; uv (OD_{max}) (cyclohexane) 243 (0.25), 284 (0.89), 352 (0.10), and 369 mμ (0.09); visible (OD_{max}) 610 (1.45), 633 (1.55), 663 (1.32), 693 (1.13), 733 (0.53), and 775 mμ (0.33). The material was not characterized further.

Method B.—The reaction of decanedioyl chloride with diethylamine, and the reaction of the presumed tetraethyldiamide product from this with azulene were carried out exactly and with the same quantities as described in method A. The maroon oil so obtained was dissolved in 8 ml of ether and to this was added 8 ml (64 mmol) of boron trifluoride etherate. The resulting red solution was added under anhydrous conditions to a stirred solution of 2 g (54 mmol) of $NaBH_4$ in 10 ml of diglyme at 0°. The mixture was stirred an additional 2 hr at 0° and then poured into 100 ml of water, and the whole was extracted with ether. The concentrate from the washed (twice with water and once with saturated NaCl) and dried extract was chromatographed over Woelm alumina. Petroleum ether–methylene chloride (9:1) eluted 25 mg of material isolated as blue crystals, mp 78–79°, which were not obtained analytically pure. The absorption spectra were consistent with the formula of 1,10-bis(1-azulyl)-decane: ir (CCl_4) 3.35, 3.45, 3.53, 6.35, 6.95, and 7.17 μ (characteristic for a 1-alkylazulene); uv (OD_{max}) (cyclohexane) 237 (0.36), 274 (0.83), 279 (0.95), 285 (0.86), 346 (0.11), and 362 mμ (0.07); visible (OD_{max}) 562 (0.61, sh), 583 (0.73), 607 (0.88), 532 (0.75), 665 (0.79), 698 (0.35), and 738 mμ (0.32). Elution with 4:1 methylene chloride–ether then gave 331 mg (31%) of **21** identical (ir, uv, and visible spectra) with the material from method A. A third fraction of 158 mg, eluted with ether, exhibited absorption spectra very similar to those of the by-product obtained in method A and was not characterized further.

N,N-Diethylpentanamide.—A solution of 25 g (0.15 mol) of valeryl bromide in 50 ml of dry ether was added over a 1-hr period to a stirred solution of 29 g (0.4 mol) of diethylamine in 50 ml of ether at 0°. The mixture was allowed to stand for 10 hr. Saturated NaCl (100 ml) was added and the whole was extracted with ether. Removal of the solvent from the washed (twice with saturated NaCl) and dried extract and distillation yielded 20 g (85%) of the amide product, bp 63–65° (1.5 mm) [lit.[42] bp 94–95° (10 mm)].

1-Pentylazulene (22). Method A.—To a solution of 384 mg (3 mmol) of azulene and 942 mg (6 mmol) of N,N-diethylpentanamide in 2 ml of dry tetrahydrofuran at 0° was added dropwise, under anhydrous conditions, 0.45 ml (5 mmol) of $POCl_3$. The mixture was stirred for 5 min at 0°, 30 min at room temperature, and 3 hr at 80°. It was then cooled to room temperature and diluted with 100 ml of water. The solution was made slightly basic with 10% KOH and was then extracted with CH_2Cl_2. The extract was washed three times with saturated NaCl, dried, concentrated, and chromatographed over acidic alumina. Petroleum ether eluted 35 mg of azulene and methylene chloride–petroleum ether (1:1) then removed a maroon oil (presumed to be crude 1-pentanoylazulene). The oil was dissolved in 3 ml of ether, 1 ml (8 mmol) of boron trifluoride etherate was added, and the resulting solution was added, under anhydrous conditions, over a 15-min period to 380 mg (10 mmol) of $NaBH_4$ in 5 ml of diglyme at 0°. The mixture was stirred an additional 30 min and then poured into 50 ml of cold 5% KOH, and the whole was extracted with ether. The extract was washed four times with 20 ml of water and once with saturated NaCl, dried, concentrated, and chromatographed over basic alumina. Petroleum ether eluted 463 mg (78%, 85% net) of **22** as a blue oil: ir (neat) 3.35, 3.45, 3.52, 6.35, 6.95, 7.16 μ (1-alkylazulene); uv (OD_{max}) (cyclohexane) 238 (0.40), 275 (1.12, sh), 279 (1.30), 298 (0.12), 347 (0.13), and 362 mμ (0.09); visible (OD_{max}) 562 (0.64, sh), 582 (0.77), 608 (0.93), 633 (0.79), 666 (0.82), 700 (0.36), and 737 mμ (0.34).

Anal. Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.75; H, 9.23.

Method B.—Azulene (256 mg, 2 mmol), N,N-diethylpentanamide (0.7 ml, 4 mmol), $POCl_3$ (0.3 ml, 0.33 mmol), and 2 ml of dry tetrahydrofuran were allowed to react and the reaction was worked up as described in method A. One-third of the maroon oil so obtained was dissolved in 10 ml of dry tetrahydrofuran and cooled to 0° with stirring. Diborane [generated in an adjacent flask by the slow addition of 380 mg (10 mmol) of $NaBH_4$ in 5 ml of diglyme to 1 ml (8 mmol) of boron trifluoride etherate] was carried into the reaction mixture by a nitrogen stream through a glass tube having a small exit orifice extending below the surface of the solution. The $NaBH_4$ addition was complete in 20 min, and the reaction mixture was stirred at 0° for an additional 30 min. Excess B_2H_6 was decomposed by the addition of a few ice chips and the mixture was then diluted with water and extracted with ether. The concentrate from the washed (twice with water and once with saturated NaCl) and dried extract was chromatographed over basic alumina. Elution with petroleum ether gave 76 mg (59%, 84% net) of **22** identical (ir, uv, and visible spectra) with the material from method A.

1,3-Dipentylazulene (23).—To a stirred solution of 404 mg (2.06 mmol) of 1-pentylazulene and 650 mg (4.15 mmol) of N,N-diethylvaleramide in 5 ml of tetrahydrofuran cooled to 0° was added dropwise under anhydrous conditions 0.32 ml (3.5 mmol) of $POCl_3$. The mixture was stirred for 5 min at 0°, 15 min at room temperature, and 1 hr at 80°. To the cooled mixture was added 100 ml of water and the solution was made slightly basic with 10% KOH. After extraction with CH_2Cl_2, the extract was washed twice with saturated NaCl and then dried. The con-

(41) T. Lieser and K. Macura, *Ann.*, **548**, 226 (1941).

(42) Y. K. Yurev and Z. U. Belyakova, *Zh. Obshch. Khim.*, **28**, 3 (1958) [*Chem. Abstr.*, **52**, 11765 (1958)].

centrate was chromatographed over acidic alumina. Petroleum ether eluted 44 mg (9%) of 1-pentylazulene and 2:1 petroleum ether–methylene chloride then removed an oil which was dissolved in 3 ml of ether. Boron trifluoride etherate (1 ml, 8 mmol) was added and the resulting solution was added over a 10-min period to a stirred solution of 380 mg (10 mmol) of $NaBH_4$ in 5 ml of diglyme at 0°. Stirring was continued for 30 min, the mixture poured into 50 ml of cold 5% KOH, and the whole was extracted with petroleum ether. The extract was washed twice with saturated NaCl, dried, concentrated, and chromatographed over acidic alumina. Elution with petroleum ether gave 410 mg (74%, 83% net) of **23** as a blue oil: uv (log ϵ) (cyclohexane) 241 (4.10), 282 (4.73), 351 (3.70), and 368 mμ (3.66); visible (ϵ) 588 (228, sh), 608 (264, sh), 632 (311), 663 (260), 695 (264), 735 (109, sh), and 776 mμ; mol wt 261 (calcd 268).

Anal. Calcd for $C_{20}H_{28}$: C, 89.49; H, 10.51. Found: 89.76; H, 10.25.

1,3-Dipropionylazulene (24).[43]—To a solution of 20 ml of propionic anhydride and 1.5 ml of $SnCl_4$ in 150 ml of CH_2Cl_2 was added 1 g of azulene dissolved in *ca.* 10 ml of CH_2Cl_2. The mixture was swirled occasionally over a 1-hr period and then shaken with 200 ml of 2 *N* hydrochloric acid. The aqueous layer was extracted with two 100-ml portions of CH_2Cl_2 and the combined extracts were washed four times with 100-ml portions of water, dried, and concentrated. Chromatography over acidic alumina and elution with *n*-hexane gave blue-green and purple fractions and then CH_2Cl_2 removed a red fraction. Rechromatography of the last and elution with *n*-hexane separated a small purple component from the red material, which was eluted with 1:1 *n*-hexane–methylene chloride and gave 114 mg (6%) of **24** as red crystals: mp 116.5–118.5°; ir ($CHCl_3$) 6.15 μ; uv (OD_{max}) (CH_2Cl_2) 259 (0.56), 289 (0.78), 309 (0.51), and 380 mμ (0.11, broad); visible (OD_{max}) 508 mμ.

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.08; H, 6.83.

1,3-Dipropylazulene (25).—To a solution of 56 mg (0.23 mmol) of 1,3-dipropionylazulene in 3 ml of 1:1 ether–diglyme was added 0.5 ml (4 mmol) of boron trifluoride etherate. The resulting solution was added dropwise under anhydrous conditions to a stirred solution of 170 mg (4.6 mmol) of $NaBH_4$ in 2 ml of diglyme at 0°. The mixture was stirred at 0° for an additional 30 min and then poured into 50 ml of cold 5% KOH and the whole was extracted with petroleum ether. The organic extract was washed twice with water and once with saturated NaCl. The concentrate from the dried solution was chromatographed over acidic alumina. Petroleum ether eluted 45 mg (91%) of **25** as a blue oil: uv (OD_{max}) (cyclohexane) 235 (0.28), 282 (0.77), 288 (0.78), 352 (0.08), and 369 mμ (0.06); visible (OD_{max}) 587 (0.47, sh), 610 (0.55, sh), 631 (0.64), 662 (0.53), 694 (0.54), 733 (0.23, sh), and 775 (0.20).

(43) This experiment was performed by Robert G. Anderson.

Anal. Calcd for $C_{16}H_{20}$: C, 90.50; H, 9.50. Found: C, 90.50; H, 9.63.

1,3-(5′-Cyano-6′-oxoundecamethylene)azulene (26).—An ethereal solution of phenyllithium[44] was determined to be 1.5 *N* by decomposing 1-ml samples of the reagent in water and titrating the aqueous solutions to the methyl orange end point with 0.1021 *N* perchloric acid. In a 2-l. three-necked flask fitted with a Trubore stirrer, dilution head, Hershberg dropping funnel, and condenser, the whole of which had been dried and filled with a nitrogen atmosphere, was placed a solution of 4 ml (6 mmol) of the phenyllithium solution and 1 l. of dry (distilled from $LiAlH_4$) ether. To the stirred solution was added through the dilution head, under reflux and nitrogen flow, 1 ml (9.5 mmol) of freshly distilled N-methylaniline. The mixture was stirred for 20 min and stirring was continued while a solution of 115 mg (0.36 mmol) of **14a** in 270 ml of dry ether was added over a period of 34 hr. The cooled (0°) reaction mixture was washed twice with water, shaken for 10 min with 50 ml of 3 *N* hydrochloric acid, and washed again with water and then with saturated NaCl. The concentrate from the dried organic solution was chromatographed over acidic alumina. Petroleum ether–methylene chloride (1:1) removed a light yellow semisolid and 2:1 petroleum ether–methylene chloride eluted a blue oil which was rechromatographed. Petroleum ether–methylene chloride (2:1) developed and eluted two bands. The second gave 15 mg of a blue oil that was not characterized. The first yielded 35 mg (31%, 5.4% from azulene) of **26** as blue crystals, mp 100–103°. The analytical sample melted at 105–107°: ir ($CHCl_3$) 4.48 (CN) and 5.80 μ; uv (log ϵ) (cyclohexane) 233 (4.39), 282 (4.65), 350 (3.71), and 368 mμ (3.65); visible (ϵ) 580 (215, sh), 605 (245), 629 (305), 660 (250), 689 (260), 732 (110), and 770 mμ (100); mol wt 289 (calcd 319).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.76; H, 7.84; N, 4.39. Found: C, 83.03; H, 8.03; N, 4.34.

Registry No.—**2**, 19981-45-4; **3**, 13502-43-7; **4**, 19981-47-6; **5**, 19981-48-7; **6**, 19981-49-8; **7**, 19981-50-1; **8a**, 19981-51-2; **8b**, 19981-52-3; **9b**, 19981-53-4; **10a**, 19981-54-5; **11a**, 19981-55-6; **11b**, 19981-56-7; **12a**, 19981-57-8; **12b**, 19981-58-9; **13a**, 19981-59-0; **13b**, 19981-60-3; **14a**, 19981-61-4; **14b**, 19981-62-5; **16**, 19981-63-6; **18**, 19981-64-7; **20**, 19981-65-8; **21**, 19981-66-9; **22**, 19981-67-0; **23**, 19981-68-1; **24**, 19981-69-2; **25**, 19981-70-5; **25**, 19981-70-5; **26**, 19981-71-6; tetraethyldiamide of decanedioyl chloride, 19268-68-9; 1-(α-hydroxyethyl)azulene, 19981-82-9; 1,10-bis(1-azulyl)decane, 19981-83-0.

(44) C. A. Walter, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 757.

The Reaction of the Grignard Reagent from Neopentyl Chloride with Benzophenone. A Nuclear Magnetic Resonance Study[1]

CORNELIS BLOMBERG,[2] RUDOLF M. SALINGER, AND HARRY S. MOSHER

Department of Chemistry, Stanford University, Stanford, California 94305

Received November 12, 1968

A study has been made of the rate of change in the nuclear magnetic resonance spectrum of a mixture of the Grignard reagent from neopentyl chloride and benzophenone in tetrahydrofuran. The expected addition reaction was complicated by the simultaneous occurrence of a radical reaction to produce neopentane and benzopinacol. Furthermore these spectra are interpretable in terms of a reaction to give an initial product which in turn undergoes further reaction with the Grignard reagent to give a new reactive species. This reactive intermediate presumably is either the alkylmagnesium alkoxide (RMgOR′) or a complex of the initial product with the Grignard reagent (RMgCl·R′OMgCl). This constitutes a direct observation of a process often postulated in the reaction of a Grignard compound. Qualitative generalizations could be made but because of these complitions it was not possible to make a quantitative kinetic analysis of the data.

We have made an investigation of the reaction of the Grignard reagent from neopentyl chloride with benzophenone using an all-glass, stopcock-free system under rigorously anhydrous and oxygen-free conditions according to techniques already described.[3] These reactants were chosen in the hope that they would furnish a suitable system for studying the kinetics of the Grignard addition reaction (eq 1) by nuclear mag-

$$(CH_3)_3CCH_2MgCl + Ph_2C{=}O \longrightarrow (CH_3)_3CCH_2(Ph_2)OMgCl \quad (1)$$

netic resonance (nmr) techniques. We reasoned that in this system (a) side reaction due to enolization would be precluded, (b) the reduction of benzophenone to benzhydrol by β-hydrogen transfer from the Grignard reagent would be impossible, (c) steric hindrance should cause the reaction to proceed at a convenient rate, and (d) the simple nmr spectra of reactants and product should permit the use of nmr techniques for following the progress of the reaction.

Figure 1A represents the 60-MHz nmr spectrum of neopentylmagnesium chloride in tetrahydrofuran.[4] The nmr spectrum of the magnesium bromide salt of diphenylneopentylcarbinol, prepared by treating the carbinol with a tetrahydrofuran solution of propylmagnesium bromide, Figure 1B, serves to locate the position for the *t*-butyl protons (a′) and the methylene protons (b′) of this alkoxide. The signal (a′) for the *t*-butyl protons is characterized by a broad base which is unexpected and which will be discussed later.

Several complications were encountered during the nmr investigations of the reactions of neopentylmagnesium chloride with benzophenone. The first of these was an unexpected radical-type side reaction[6] (eq 2)

$$(CH_3)_3CCH_2MgCl + 2Ph_2C{=}O + THF \longrightarrow C(CH_3)_4 + Ph_2C(ClMgO)-C(OMgCl)Ph_2 + ? \quad (2)$$

which gave neopentane and (on hydrolysis) benzopinacol. The 60-MHz nmr spectrum of a reaction mixture of equimolar amounts of neopentylmagnesium chloride and benzophenone in perdeuterated THF,[7] 24 hr after mixing, is shown in Figure 1C. The sharp singlet for the protons (e) of neopentane[8] was so close to the signal for the *t*-butyl protons (a) of the unreacted Grignard compound that neither could be used for accurate kinetic measurements (compare Figures 1A, 1C, 1D, and 2).

A second complication was that the change of the nmr spectrum of the reaction mixture during the progress of the reaction was considerably more complex than the simple stoichiometric eq 1 would indicate. This is very clearly illustrated in Figure 1D, which shows the 60-MHz nmr spectrum of a reaction mixture from diphenylneopentylcarbinol and excess neopentylmagnesium chloride in THF. This solution shows the signals for neopentane (e), the alkoxide of the carbinol (a′, b′), and unreacted neopentylmagnesium chloride (a, b) as well as those for the solvent (c). This spectrum can not be reconstructed by adding together the spectra of Figures 1A and 1B and that of neopentane. The signal for the *t*-butyl protons (a′) in the reaction product shows as three peaks instead of a singlet as is observed in the nmr spectrum of a solution of the magnesium bromide salt of diphenylneopentylcarbinol (Figure 1B).[9] In addition, the methylene protons in the excess Grignard reagent appear as two unequal and somewhat broad signals (Figures 1D and 2; b, 19 cps upfield from TMS, and bb, 29 cps upfield from TMS

(1) We gratefully acknowledge support of these studies by the National Science Foundation, Grant GP 6738.

(2) On leave from the Vrije Universiteit, Amsterdam, The Netherlands.

(3) A. D. Vreugdenhil and C. Blomberg, *Rec. Trav. Chim. Pays-Bas*, **82**, 453 (1963).

(4) Recently House, Latham, and Whitesides,[5] in an extensive paper on nmr spectra of several organomagnesium compounds, reported (in their Experimental Section) some of their results obtained with diethyl ether solutions of neopentylmagnesium chloride and of dineopentylmagnesium. The authors did not undertake further investigations on these solutions "because of apparent presence of alkoxide impurities." From Table XII in their paper it follows that at 60 MHz in diethyl ether solution the *t*-butyl absorption peak appears at 70 cps downfield from internal TMS standard (50 cps in THF as shown in Figure 1A, signal a, according to our studies) whereas methylene proton absorption occurs at 18 cps upfield for the Grignard compound and at 20.0–20.5 cps upfield for the dialkylmagnesium compound (29 cps, Figure 1A–b and 31 cps, Figure 3B–b, respectively, in THF according to our studies).

(5) H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, **32**, 2481 (1967).

(6) C. Blomberg and H. S. Mosher, *J. Organometal Chem.*, **13**, 519 (1968).

(7) The solvent signals (c) in Figure 1C are due to a small amount of THF-d_7 and isotopically normal THF which was incompletely removed from the original Grignard reagent which was prepared in isotopically normal THF, the solvent removed under high vacuum, and perdeuterated THF added.

(8) Identified[6] by comparison with the nmr spectrum of an authentic sample; also see Figure 1D. Mass spectral analysis of a sample of gas isolated from this reaction showed an incorporation of deuterium, which establishes the origin of the additional hydrogen in the neopentane.

(9) During preliminary investigations of several other reactions of aliphatic Grignard compounds with ketones this same phenomenon was observed. Namely, the signals for the protons of the alkoxy group and the Grignard reagent were more complicated than expected based upon the stoichiometric eq 1 alone.

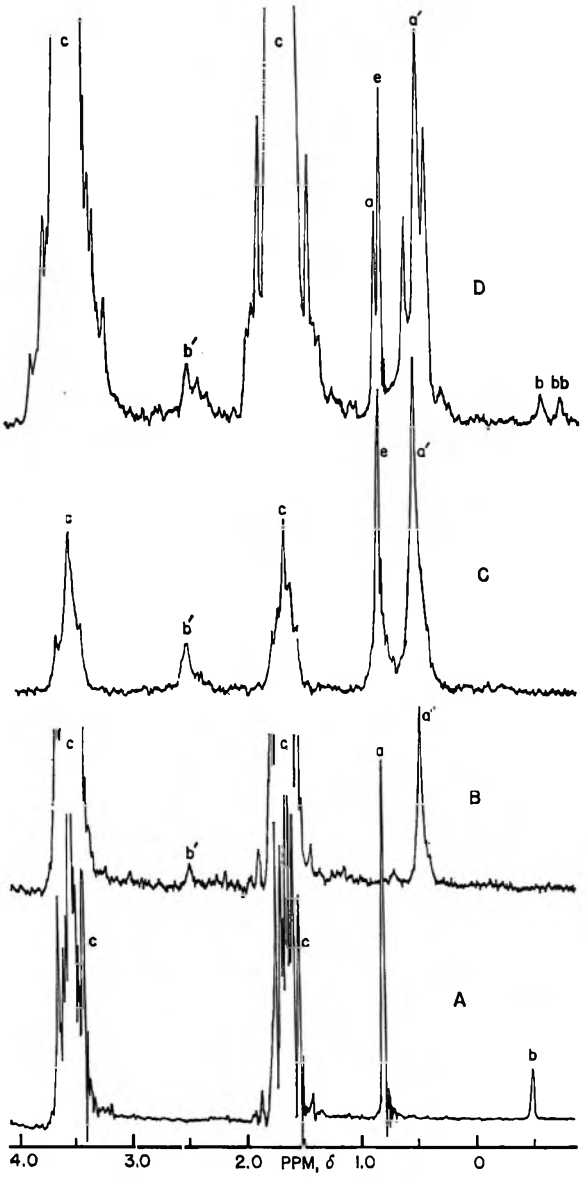


Figure 1.—A is the nmr spectrum of 0.74 *N* neopentylmagnesium chloride in THF. The *t*-butyl protons [$(CH_3)_3C$–] are designated as a, the methylene protons [$-CH_2Mg-$] as b, and the solvent protons as c. Aromatic signals are not shown. B is the nmr spectrum of the magnesium bromide salt of diphenylneopentylcarbinol in THF, 1.0 *N*, prepared by the reaction of propylmagnesium bromide with the carbinol. The *t*-butyl protons [$(CH_3)_3C$–] are designated a′, the methylene protons [$-CH_2CPh_2-$] as b′. C is the 60-MHz spectrum of a reaction mixture from equimolar amounts of neopentylmagnesium chloride and benzophenone in perdeuterated THF, 0.74 *N*, 24 hr after mixing. The neopentane protons [$(CH_3)_4C$] are designated as e. Designation of signals a′, b′, and c are the same as in A, B, and D. D is the 60-MHz spectrum of a reaction mixture from equal volumes of neopentylmagnesium chloride (0.74 *N*) and diphenylneopentylcarbinol (0.67 *N*) in THF.

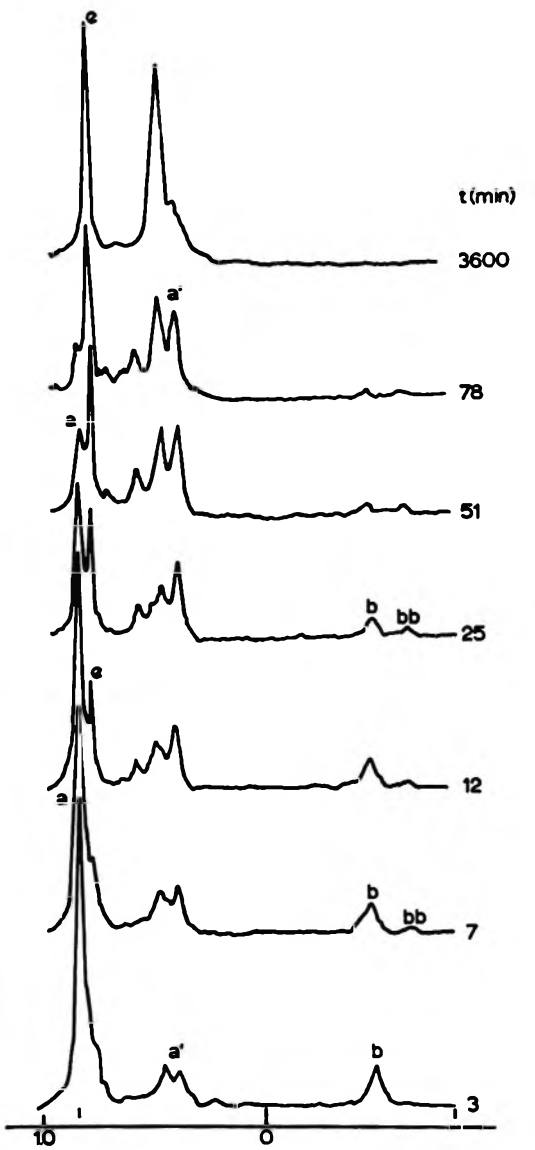


Figure 2.—Change of 60-MHz nmr spectra with time; equimolar mixture of neopentylmagnesium chloride and benzophenone in THF, 0.74 *N*, 20°. Designation of signals is as in Figures 1 and 3.

standard) compared with the lone signal shown in Figure 1A.[10]

Figure 2 represents part of several nmr spectra of a reaction mixture of molar equivalents of neopentylmagnesium chloride and benzophenone in THF at 20° taken at different time intervals. Several trends are evident. (1) Peak a, due to the *t*-butyl protons of unreacted Grignard reagent, slowly decreases. (2) At the same time peak e, due to the protons in neopentane, increases. (3) The broad peak b, due to the methylene protons of the Grignard reagent, decreases and at the same time a second broad peak, bb, forms and ultimately disappears. Three minutes after mixing, peak b has broadened (*cf.* Figures 1A and 2), probably owing to fast complexation with the ketone. (4) A doublet peak, a′, is evident 3 min after mixing and as the reaction proceeds the signals in this region increase in intensity and become more complex but finally change back to a single major peak with a broad base after several hours time.

Quantitative kinetic analysis of these complex changes based on the 60-MHz nmr spectra was not feasible. The situation was improved but not resolved at 100 MHz. Qualitatively, however, we interpret the changes in the following manner. Simultaneous reactions, represented by eq 1 and 2, are taking place. The unusual free-radical nature of the reaction leading to neopentane and benzopinacol has been discussed.[6] The initial addition reaction, represented by eq 1 (in which coordinated ether molecules are not shown),

(10) In their paper on nmr spectra of organomagnesium compounds, House, Latham, and Whitesides[4,5] also recorded a second absorption peak for methylene protons vicinal to a carbon–magnesium bond when alkoxides were present in the solution.

produces an alkoxide, R'OMgCl. This initial alkoxy product reacts with the Grignard reagent, RMgCl, either by complexing as in eq 3 or by disproportionation as in eq 4 (or by both) to give a second form of a reactive organomagnesium reagent as revealed by the developing signal bb; the methylene protons of the carbon attached to magnesium, in either or both products of eq 3 and 4, must give a signal (bb) different from that of the unreacted initial Grignard reagent. The products from reaction 3 and/or 4 compete with the original Grignard reagent in the reactions with benzophenone.

$$\text{R'OMgCl} + \underset{\text{RMgCl}}{\text{RMgCl}} \rightleftharpoons \text{R'OMgCl} \quad (3)$$

$$\text{R'OMgCl} + \text{RMgCl} \rightleftharpoons \text{R'OMgR} + \text{MgCl}_2 \quad (4)$$

House, Latham, and Whitesides[5] have observed similar phenomenon in the nmr spectrum of the diethyl ether solution of dineopentylmagnesium, containing alkoxide impurities as well as in the nmr spectra of the diethyl ether solution of the methylmagnesium alkoxide of 3-methyl-3-pentanol. In the latter case these authors observed collapse of the two signals after the addition of 0.5 mol equiv of magnesium bromide or after dilution with "the better solvating solvent, tetrahydrofuran." Considering these and our own observations, one is struck by the difference in behavior of the two alkoxides: whereas the presence of magnesium bromide or THF catalyzes the exchange of alkyl or alkoxy groups or breaks complexes between organometallic reagents and magnesium alkoxides among the methylmagnesium species, such an exchange is not observed among neopentylmagnesium species, at least not catalyzed by magnesium chloride and/or THF. Furthermore, from the spectra given in Figure 2 it may be concluded that the alkoxy products, represented in eq 3 and 4, must give absorption for the *t*-butyl protons of the carbinol moiety which are not identical with those of the alkoxy product, represented in eq 1.

An additional alkoxy species which may further contribute to the complexity of the signal a′ of the *t*-butyl group in the alkoxide may be formed by the disproportionation of the initial alkoxy group according to eq 5 to give a dialkoxymagnesium. The nmr spectrum of the reaction mixture of benzophenone and dineopentylmagnesium (containing 12 mol % magnesium chloride) sheds some light on the problem of complexation and equilibration of different alkoxides species (Figure 3). Figure 3A is the nmr spectrum of the reaction mixture from 1 mol of dineopentylmagnesium and 2 mol of benzophenone. It is seen that the spectrum for the *t*-butyl protons [a′ in $(RO)_2Mg$] made in this manner is very different than that for the corresponding alkoxide (a′ in Figures 1B and 1C) made from the usual Grignard reagent. It should be noted again that neopentane is formed in this reaction mixture, signal e.

$$2\text{R'OMgCl} \rightleftharpoons (\text{R'O})_2\text{Mg} + \text{MgCl}_2 \quad (5)$$

A peculiar observation was made concerning the nmr spectrum of the reaction mixture of neopentylmagnesium chloride with 2 molar equiv of benzophenone. The spectrum originally observed differed only slightly from the usual spectrum such as given in Figure 1C (or Figure 2 after 3600 min). However, 31 days after mixing the two reactants, a sharp signal, a few cycles per second upfield from the neopentane absorption e, had appeared at the expense of the original signal a′. This new signal a″ is located at almost the same position as a peak in the region of the nmr spectrum of the reaction mixture of dineopentylmagnesium with benzophenone irrespective of the molar ratios of these two reagents (Figure 3A and 3B). It is presumed that under the influence of excess benzophenone the equilibrium, represented by eq 5, is shifted to the right. This phenomenon was not observed in reaction mixtures of *equivalent* amounts of neopentylmagnesium chloride and benzophenone after 120 days.

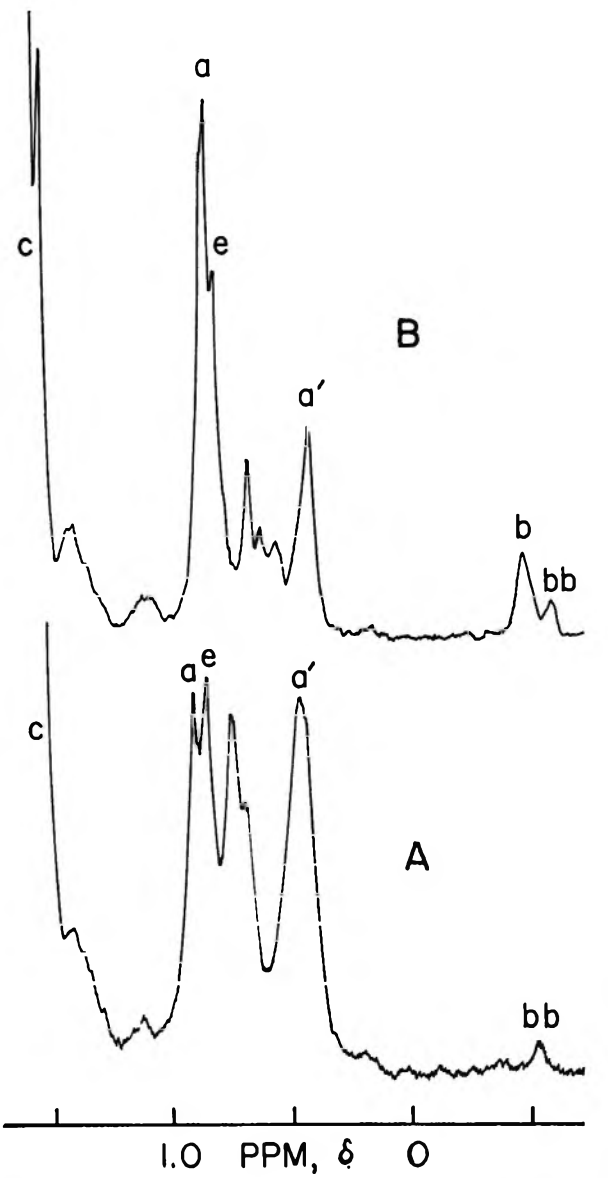


Figure 3.—Spectra of mixtures of dineopentylmagnesium, 0.57 *M*, and benzophenone; molar ratio 1:2 in A and 2:1 in B. Designation of signals is same as in Figures 1 and 2.

The reactivity of products such as represented by eq 3 and/or 4 should differ appreciably from that of the initial Grignard reagent.[11] Thus kinetic analysis of a reaction such as this will be complicated unless limited

(11) M. S. Singer, R. M. Salinger, and H. S. Mosher, *J. Org. Chem.*, **32**, 3821 (1967); J. Billet and S. G. Smith, *J. Amer. Chem. Soc.*, **90**, 4108 (1968) and references therein.

to initial rates or to reactions in which one reagent is in considerable excess. The present nmr analysis therefore has uncovered complexities to this reaction that kinetic studies, based upon product analysis, could not hope to reveal.

Experimental Section

Preparation of Organomagnesium Compounds.—Preparation and handling of the organomagnesium compounds was performed in a glass-to-glass sealed high vacuum apparatus as described previously.[3] Transfers were made *via* break-seal arrangements and samples were removed by sealing off side arms without use of stopcocks.

Neopentyl chloride, 100 mmol, was magnetially stirred with magnesium crystals,[12] 110 mg-atom, in 100 ml of tetrahydrofuran; no reaction took place during 4 days of continuous stirring although a cloud of powdered magnesium made the solution gray. On the addition of 6 mmol of 1,2-dichloroethane a slow reaction took place. The yield of neopentylmagnesium chloride was 85% after 7 days. The solution contained 5 mol % magnesium chloride and unreacted organic halides. After standing a few weeks a clear water-white solution was obtained which was freed from the sediment by decanting in the sealed vacuum system into another vessel and from which all volatile material was removed by cooling one arm of the apparatus with liquid nitrogen while gradually increasing the temperature in the other from 100 to 150° during a 5-hr period. New tetrahydrofuran was distilled onto the glassy residue. The nmr spectra of the solution, which was 0.85 *M* in RMgX and which contained 5 mol % magnesium chloride, showed that no unreacted halides were present. Small ampoules, *ca.* 2 ml, were filled with this solution for use in nmr work.

(12) The authors gratefully acknowledge the gift of sublimed magnesium from the Dow Chemical Co. It had the following maximum limits of elemental impurities in parts per million: Al, 1; Cu, 1; Fe, 4; Mn, 2; Ni, 4; Pb, 10; Si, 10; Zn, 100; Ba, 1; Ca, 18; K, 5; K, 5; Na, 6; Sn, 1.

On cooling of the neopentylmagnesium chloride solution in a carbon dioxide–acetone bath, beautiful crystals were obtained which contained mainly magnesium chloride. When the mother liquors were decanted and cooled anew, again crystals were formed which contained an excess of magnesium chloride over dineopentylmagnesium. This second mother liquor was again decanted from the crystals and found to contain 0.60 mmol of dineopentylmagnesium and 0.15 mmol of magnesium chloride/ml (total volume was 7 ml). To precipitate the total amount of 1.1 mmol of magnesium chloride 2.2 mmol of dioxane was added. After 3 weeks a solid white precipitate was formed from which the mother liquor (4.5 ml) was decanted; it contained 0.57 mmol of dineopentylmagnesium and 0.07 mmol of magnesium chloride/ml and was used without further purification.

Nmr Measurments.—Use was made of nmr tubes provided with a glass constriction to make sealing possible. Filling of the tubes was performed under high vacuum as usual and no special difficulties were encountered during such manipulations. Benzophenone was distilled from a side tube into the nmr tube containing the Grignard solution which was cooled to −80° (causing the formation of beautiful crystals). The distillation path was no longer than 10 cm and use was made of a "hot air gun" to control the distillation and solidification of the benzophenone on to the cooled glass wall above the THF solution. The tube was sealed, and the mixing of the reagents was done immediately before nmr measurements were started. In all cases reddish brown color appeared which changed to orange-yellow during the course of the reaction.

Registry No.—Neopentylmagnesium chloride, 13132-23-5; benzophenone, 119-61-9; magnesium bromide salt of diphenylneopentylcarbinol, 19978-29-1; diphendiphenylneopentylcarbinol, 19978-30-4; dineopentylmagnesium, 19978-31-5.

Acknowledgment.—We thank Dr. Lois Durham for her cooperation and advice in collecting the nmr spectral data.

The Oxidative Coupling of Phenols Using Vanadium Tetrachloride and Vanadium Oxytrichloride

W. L. CARRICK, G. L. KARAPINKA, AND G. T. KWIATKOWSKI

Union Carbide Corporation, Chemicals and Plastics, Operations Division, Bound Brook, New Jersey 08805

January 28, 1968

The oxidation of most simple phenols and some aniline deivatives with vanadium tetrachloride or vanadium oxytrichloride affords dimeric products which are coupled predominantly at the *para* position. For example, admixture of equimolar quantities of phenol and vanadium tetrachloride in an inert solvent followed by hydrolysis led to the isolation of 4,4′-diphenyl, 2,4′-diphenol, and 2,2′-diphenol in an approximate ratio of 8:4:1 and an over-all yield of 55–65%. The remainder of the product mixture was composed of unreacted phenol and <5% of chlorinated diphenols. Phenol itself was not oxidized by vanadium oxytrichloride, under the condition of vanadium tetrachloride oxidation; however, those phenol derivatives with lower oxidation potentials were coupled by this reagent. Thus, 1- and 2-naphthol reacted smoothly with vanadium oxytrichloride to produce 4,4′-dihydroxybinaphthyl and 2,2′-dihydroxybinaphthyl in 56 and 65% yields, respectively. The oxidative coupling reaction is believed to occur by a rearrangement of electrons in a complex containing at least two phenoxide (or phenol) residues and at least one metal center. Evidence in support of the existence of vanadium phenoxides has been obtained. The selectivity of the coupling reaction may be interpreted in terms of a polar or ionic transition state in which charges are developed in the aromatic ring.

The oxidative coupling of phenolic compounds has received considerable attention owing both to its utility as a synthetic reaction and its proposed involvement in the biosynthesis of a number of classes of natural products.[1] To date, the oxidation of the most of the simple phenols and naphthols has been studied with a variety of reagents and, in general, the products are complicated mixtures of dimeric, polymeric, and quinonoid compounds.[2] In most cases, both carbon to carbon and carbon to oxygen coupling occurs, although, depending on the oxidant and on the experimental conditions, some selectivity can be attained.[3] We wish to report here results on two unique oxidizing agents, vanadium tetrachloride and vanadium oxytrichloride, which couple phenols and some aromatic amines predominantly at the *para* position and afford

(1) A recent survey of phenol oxidations is available: "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, Inc., New York, N. Y., 1967.

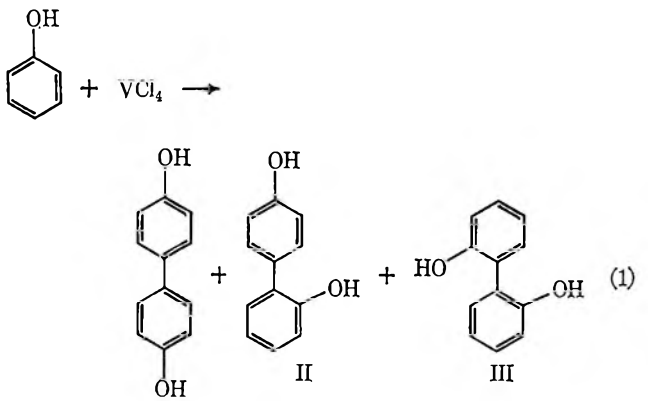
(2) Leading references can be found in H. Musso, ref 1, Chapter 1.

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

mainly dimeric products. These reagents grossly simplify the preparation 4,4′-diphenols and should find wide applicability throughout the area of phenolic oxidative coupling.

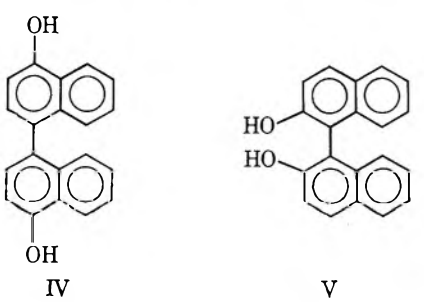
Results

Coupling of Phenols with Vanadium Tetrachloride.—Admixture of equimolar quantities of phenol and vanadium tetrachloride in an inert solvent produced a black, finely dispersed precipitate with concomitant hydrogen chloride evolution. Hydrolysis of the reaction mixture and extraction led to the isolation of three products, identified as 4,4′-diphenol (I), 2,4′-diphenol (II), and 2,2′-diphenol (III) (eq 1) in an approximate ratio of 8:4:1 and an over-all yield of 55–65%. The



remainder of the product mixture was composed of unreacted phenol and <5% chlorinated biphenols. Products derived from carbon–oxygen coupling were never observed. In addition, a material balance study showed that the above products accounted for 96% of the initially charged phenol. Investigation of the aqueous layer indicated that vanadium(III) and -(IV) species were present; however, the relative amounts of both species was not determined.

The majority of the phenols which were treated with vanadium tetrachloride reacted (see Table I). Both 1- and 2-naphthols reacted cleanly to afford 4,4′-dihydroxybinaphthyl (IV) and 2,2′-dihydroxybinaphthyl (V) in 40 and 38% yields, respectively.



Reaction of the cresols with vanadium tetrachloride generally produced resinous materials from which dicresols could be isolated. For example, oxidation of *o*-cresol gave a 26% yield of 3,3′-dimethyl-4,4′-dihydroxybiphenyl and a deep blue material, possibly the quinhydrone of the above bisphenol and the corresponding diphenoquinone. Oxidation of *m*- and *p*-cresols yielded resinous mixtures from which only small quantities of 2,2′-dimethyl-4,4′-dihydroxybiphenyl and 2,2′-dihydroxy-5,5′-dimethylbiphenyl could be obtained. The resinous products from *p*-cresol also contained a small amount of "Pummerers ketone" (VI), a well-known oxidation product of *p*-cresol.[4,5] Vanadium tetrachloride reacted with 2,6-xylenol to afford a 6% yield of 3,3′,5,5′-tetramethyl-4,4′-dihydroxybiphenyl and an 18% yield of the corresponding quinhydrone. With 2,4,6-trimethylphenol, a vigorous evolution of hydrogen chloride occurred. However, on hydrolysis only the unreacted phenol was recovered. No oxidation products could be detected. When sodium phenoxide was used in place of phenol, chlorinated diphenols and other high boiling compounds were the major products.

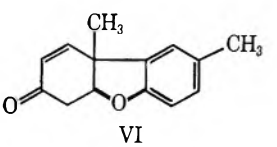
TABLE I

OXIDATION OF SUBSTITUTED AROMATICS WITH VANADIUM TETRACHLORIDE

(substrate/VCl_4, 1:1; 25°; CCl_4)

Substrate	Product	Yield %
Phenol	4,4′-Dihydroxybiphenyl	34
	2,4′-Dihydroxybiphenyl	18
1-Naphthol	4,4′-Dihydroxybinaphthyl	40
2-Naphthol	2,2′-Dihydroxybinaphthyl	38
p-Cresol	2,2′-Dihydroxy-5,5′-dimethylbiphenyl	Small quantity
m-Cresol	2,2′-Dimethyl-4,4′-dihydroxybiphenyl	Small quantity
o-Cresol	3,3′-Dimethyl-4,4′-dihydroxybiphenyl	26
2,6-Xylenol	3,3′,5,5′-Tetramethyl-4,4′-dihydroxybiphenyl	6
2,4,6-Trimethylphenol	No reaction	
o-Chlorophenol	Unidentified products	Trace
N,N-Dimethylaniline	N,N,N,N-Tetramethylbenzidine	52
Diphenylamine	N,N-Diphenylbenzidine	43
Aniline	Aniline black (?)	Trace
Quinaldine	No reaction	
Anisole	No reaction	
Benzoic acid[a]	Trichloroacetophenone (?)	Trace
Ethyl benzoate	No reaction	

[a] At 65°.

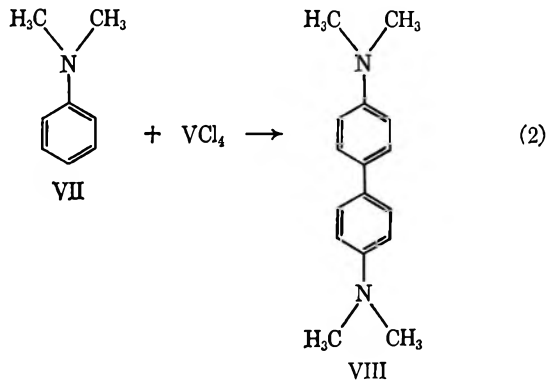


VI

Benzene, toluene, anisole, phenyl acetate, and ethyl benzoate all failed to react with vanadium tetrachloride under the standard conditions. Aniline and aniline derivatives were oxidatively coupled by vanadium tetrachloride. Thus, N,N-dimethylaniline (VII) afforded a 52% yield of N,N,N′N′-tetramethylbenzidine (VIII) (eq 2) and diphenylamine gave a 43% yield of N,N′-diphenylbenzidine. It is interesting to note that, in the case of N,N-dimethylaniline, smooth *para* coupling occurred in spite of the fact that the compound is a tertiary amine (in contrast with anisole, which does not react). Under the same conditions, aniline was oxidized to an unidentified black product, most probably "aniline black," whose infrared (ir) spectrum

(4) R. Pummerer, D. Melamed, and H. Puttfarcken, *Ber.*, **55**, 3116 (1922).

(5) K. Bowden and C. H. Pelce, *J. Chem. Soc.*, 2249 (1950).



VII VIII (2)

showed *para* substitution. Reaction of 2-methylquinoline with vanadium tetrachloride failed to produce coupled products.

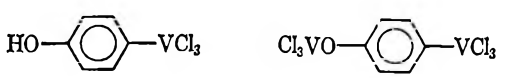
The yield of coupled products was found to be insensitive to the ratio of the reactants. Variations in the ratio of phenol to vanadium tetrachloride in the range of 4:1 to 1:4 failed to increase the yield of diphenol (Table II). The amount of hydrogen chloride liberated

TABLE II
REACTION OF PHENOL WITH VANADIUM TETRACHLORIDE (25%; CCl_4)

C_6H_5OH/VCl_4	Yield of *p,p'*-diphenol[a]	HCl/VCl_4	HCl/phenol
1	38	1.2	1.2
2	46	1.5	0.8
3	45	2.0	0.7
0.5	46	0.7	1.4

[a] Yields are based on the amount of the limiting reagent.

was, however, dependent on the ratio of phenol to vanadium tetrachloride (Table II). In all cases, more hydrogen chloride was evolved than could be accounted for solely on the basis of two molecules of hydrogen chloride being liberated per molecule of dimer produced. This indicates that vanadium to oxygen or vanadium to carbon bonds are also being formed with liberation of hydrogen chloride. To investigate the possibility that carbon to vanadium bonds such as in IX or X are formed, the mixture was hydrolyzed with deuterium oxide. The ir spectrum of the recovered



IX X

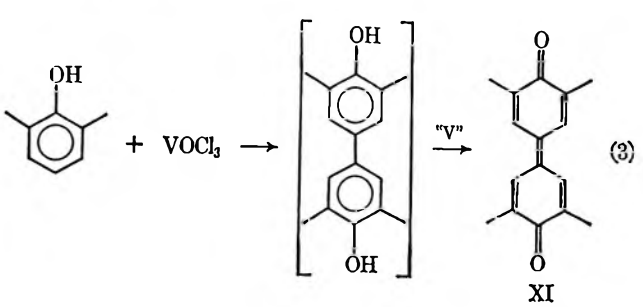
phenol did not show deuterium–carbon absorption, thus ruling out the presence of any substantial concentration of intermediates containing a carbon to vanadium bond at the time of hydrolysis.[6] The above facts show that the majority of the hydroxyl groups at the end of the reaction are tied up as vanadium phenoxides; however, this experiment does not exclude the intermediacy of vanadium–carbon bonds during the reaction.

As reaction solvents, carbon tetrachloride, chloroform, chlorobenzene, benzene, and cyclohexane have all been employed. The solid complex formed in the reaction of phenol with vanadium tetrachloride is totally insoluble in these solvents. For example, filtration before hydrolysis of the product mixture (under nitrogen) from reaction in carbon tetrachloride afforded a clear filtrate which was shown to be devoid of phenolic (phenol or diphenol) and vanadium(III) and -(IV) species. The elemental analysis of the precipitate was not consistent with any one structure, but suggested that the product was a complex mixture containing many components.

In control experiments, it was found that vanadium dichloride, vanadium trichloride, and hydrogen chloride do not interfere with the coupling reaction. However, both *o,o'*- and *p,p'*-diphenol react with vanadium tetrachloride and inhibit the phenolic oxidation reaction. Thus, addition of an equivalent amount of vanadium tetrachloride to a solution of *p,p'*-diphenol in chlorobenzene resulted in the liberation of hydrogen chloride and the formation of a black precipitate. Upon hydrolysis, the diphenol was recovered quantitatively. If 1 equiv of phenol is added to the above mixture before hydrolysis, little reaction takes place and 85% of the phenol is recovered unchanged. Attempts to increase the yield of coupled products by reoxidating the complexed vanadium(III) species with atmospheric oxygen, cupric chloride, stannic chloride, vanadium oxytrichloride, and other oxidizing agents were unsuccessful.

Coupling of Phenols with Vanadium Oxytrichloride.—Reaction of phenol with vanadium oxytrichloride under the conditions of the vanadium tetrachloride reaction resulted in the liberation of hydrogen chloride, but on hydrolysis phenol was completely recovered. When the reaction was carried out in refluxing chlorobenzene or refluxing phenol for extended periods of time, low yields of diphenol were obtained (<5%). The formation of diphenol, albeit in low yield, suggested that vanadium oxytrichloride may be a useful reagent for the oxidation of the more reactive phenols. Indeed, vanadium oxytrichloride reacted cleanly with 1- and 2-naphthols to produce 4,4'-dihydroxybinaphthyl (IV) and 2,2'-dihydroxybinaphthyl (V) in 56 and 65% yields, respectively (Table III). The course of the reaction was similar to the vanadium tetrachloride reaction in that hydrogen chloride was vigorously evolved and a dark precipitate was formed.

Oxidation of cresols with vanadium oxytrichloride gave a resinous material whose ir spectrum showed *para* substitution. Attempts to isolate bicresols from these materials were not successful. With 2,6-xylenol, a 38% yield of 3,3', 5,5'-tetramethyl-4,4'-diphenoquinone (XI) was obtained (eq 3). In this case, no diphenol was isolated.



XI (3)

Vanadium oxytrichloride oxidized diphenylamine to an unidentifiable polymeric material. With N,N-dimethylaniline in an aqueous medium, a low yield of N,N,N',N'-tetramethylbenzidine was obtainable along

(6) It is possible that carbon–vanadium-bonded species do not hydrolyze to give carbon–hydrogen bonds: J. M. Davidson and C. Triggs, *J. Chem. Soc., A*, 1324 (1968).

TABLE III
OXIDATION OF SUBSTITUTED AROMATICS WITH VANADIUM OXYTRICHLORIDE

Substrate	Product	Yield %
Phenol	Diphenol	
1-Naphthol	4,4′-Dihydroxybinaphthyl	56
2-Naphthol	2,2′-Dihydroxybinaphthyl	65
m-Cresol	Unidentified polycresol	
2,6-Xylenol	3,3′,5,5′-Tetramethyl-4,4′-diphenoquinone	38
Diphenylamine	Unidentified polymer	
Ethyl benzoate[a]	No reaction	

[a] At 65°.

with polymeric products. The use of water as solvent offers certain advantages; for example, the vanadium oxtyrichloride can be used in catalytic amounts and reoxidized with potassium chlorate.

Discussion

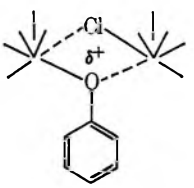
Although the mechanism for the coupling of phenols with vanadium tetrachloride or vanadium oxytrichloride has not been completely elucidated, certain factors are evident. The reactivity of free phenols and the relative inertness of *ortho*-substituted phenols and aromatic hydrocarbons indicates that the hydroxy group on phenol has a significant influence on the course of the reaction. This can be attributed to both the higher reduction potential of the free phenols and the necessity for formation of oxygen to vanadium bonds. A considerable amount of evidence has been obtained which indicates that vanadium phenoxides with complex structures are formed during the reaction. The fact that more hydrogen chloride is evolved than can be accounted for solely by the loss of two molecules of hydrogen chloride per molecule of dimer produce strongly suggests that vanadium phenoxides are present. The deuterium oxide quenching experiments in which no carbon–deuterium bonds were detectable is also suggestive. Further support for the intermediacy of vanadium–oxygen bonds was obtained in an experiment in which trichlorotitanium phenoxide was allowed to react with vanadium tetrachloride to afford a 41% yield of 4,4′-diphenol (eq 4) and a 38% yield of hydrogen chloride. The lack of influence by the trichlorotitanium substituent points to the following exchange reaction 5 in which the trichlorovanadium phenoxide is

$$C_6H_5OTiCl_3 + VCl_4 \longrightarrow TiCl_4 + \text{diphenol} + V^{III}\ \text{species} \quad (4)$$

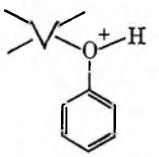
$$C_6H_5OTiCl_3 + VCl_4 \rightleftharpoons C_6H_5OVCl_3 + TiCl_4 \quad (5)$$

then the active coupling species or an intermediate leading to one. If the normal reaction pathway involved a Friedel–Crafts-type metalation of the aromatic nucleus, then one would expect the trichlorotitanium substituent to have a significant effect on the course of the reaction.

The oxidative coupling is believed to occur by a rearrangement of electrons in a complex containing at least two phenoxide (or phenol) residues and at least one metal center. The selectivity of the coupling reaction may be interpreted in terms of a polar or ionic transition state in which charges are developed in the aromatic rings. Intermediates related to XII and XIII could serve to polarize the aromatic ring and distribute a quasicationic charge to the 2 and 4 positions of one of the aromatic residues. The existence of intermediates such as XIII is suggested by the data on the evolution



XII



XIII

of hydrogen chloride from the reaction mixture (Table II). It is also plausible that vanadium to carbon bonds of either the π or σ types are involved in the coupling process. Organovanadium compounds of the types $C_6H_5VOCl_2$ and $C_6H_5VCl_3$ were previously prepared in these laboratories and were found to decompose spontaneously to biphenyl and the lower valence vanadium halide[7] (eq 6).

$$2C_6H_5VX_n \longrightarrow C_6H_5C_6H_5 + 2VX_n \quad (6)$$

Mention should be made at this point of some interesting results obtained by other workers with molybdenum oxytetrachloride. Larson and Moore have found that molybdenum oxytetrachloride oxidizes aromatic compounds with specific coupling at the *para* positions.[8] For example, reaction of molybdenum oxytetrachloride with refluxing phenol afforded a 19.6% yield of 4,4′-diphenol and reaction with refluxing benzene gave a 40% yield of poly-*p*-phenylene. Under our conditions (admixture of equimolar quantities of phenol and molybdenum oxytetrachloride in carbon tetrachloride), the following product distribution, accounting for 65% of the initially charged phenol, was obtained after hydrolysis: 54% phenol, 12% *o*- and *p*- chlorophenols, 5% *o,o′*-diphenol, 1% p,p′-diphenol, and 28% *p,p′*-diphenol. The remaining 35% was made up of polymeric products.

At present, the outstanding mechanistic questions seem to be the following: (1) whether the reactive intermediates leading to coupled products are vanadium phenoxides or vanadium to carbon bonded species; (2) whether oxidation occurs by a two-electron or a one-electron transfer from phenol to a metal center; and (3) what factors are responsible for the incomplete oxidation of phenol to diphenol. One can regard the resolution of these mechanistic problems as a useful, although difficultly attainable, goal. Clearly, vanadium tetrachloride and vanadium oxytetrachloride are extremely useful reagents for the preparation of diphenols and diaminobiphenyls by direct coupling.

Experimental Section

General Reaction Procedure.—Into a 250-ml, two-neck, round flask equipped with a magnetic stirrer was placed 100 ml of dry solvent, usually carbon tetrachloride. One neck was connected to a bubble counter filled with carbon tetrachloride, and the other was plugged with a serum stopper. After 40 mmol of aromatic substrate was introduced, the system was thoroughly purged with nitrogen and 40 mmol of transition

(7) W. L. Carrick, W. T. Reichle, F. Pennella, and J. J. Smith, *J. Amer. Chem. Soc.*, **82**, 3887 (1960).
(8) M. L. Larson and F. W. Moore, *Inorg. Chem.*, **5**, 801 (1966).

metal compound solution was then introduced *via* a hypodermic syringe. After the initial reaction was complete, the mixture was stirred for an additional hour and then decomposed with 100 ml of sulfuric acid. If an insoluble reaction product was formed, it was filtered, crystallized from a suitable solvent, and identified by its melting point and ir spectrum. The carbon tetrachloride layer was separated and evaporated to dryness. The dry residue was treated with an excess of hot water to wash away any starting material. The product was purified by crystallization or sublimation and identified by its melting point and ir spectrum.

Reaction of Phenol with Vanadium Tetrachloride.—Into the apparatus described above was placed 3.8 g (40 mmol) of distilled phenol and 100 ml of dry carbon tetrachloride. After the system was purged with nitrogen, the stirring was started and 40 mmol of vanadium tetrachloride in 15 ml of carbon tetrachloride was introduced. The reaction mixture turned dark, vigorous evolution of hydrogen chloride started, and an insoluable dark residue formed.[9] An exotherm of about 10° accompanied the reaction. The evolution of hydrogen chloride stopped after about 5 min. After the reaction mixture was stirred for a total of 1 hr, it was decomposed with 100 ml of sulfuric acid; a greenish blue acidic layer, colorless carbon tetrachloride layer, and a white crystalline interlayer developed. The white solid was filtered, washed with water, and recrystallized from alcohol to yield 1.1 g (30%) of 4,4′-dihydroxybiphenyl, mp 275–278° (lit.[10] mp 274–275°). The ir spectrum and vpc retention times were identical with those for an authentic sample of 4,4′-dihydroxybiphenyl.

In a second experiment, the reaction mixture was worked up by pouring it into 50 ml of 1 *N* hydrochloric acid and extracting exhaustively with ether. Vpc analysis using a 3-m column packed with 3% O.V. 1 on Chromosorb P indicated that the following components were present: 39% phenol, 4% 2,2′-dihydroxybiphenyl, 18% 2,4′-dihydroxybiphenyl, 34% 4,4′-dihydroxybiphenyl, and 5% higher boiling products.

Reaction of N,N-Dimethylaniline with Vanadium Tetrachloride.—Into the apparatus described under the general reaction procedure was placed 100 ml of dry carbon tetrachloride and 5.1 ml (40 mmol) of distilled N,N-dimethylaniline. After the system was purged with nitrogen the stirring was started and 40 mmol of vanadium tetrachloride was added. A dark precipitate formed immediately. The reaction mixture was stirred for 1 hr and then decomposed with 100 ml of sulfuric acid. The aqueous layer was separated and basified with 10% sodium hydroxide. The dark green residue was filtered, washed with water, and dried. This residue was then extracted with ether in a soxhlet for 2 days. On evaporation of ether, 2.2 g of N,N,N′,N′-tetramethylbenzidine was obtained: mp 194° (crystallized from alcohol).

Reaction of 1-Naphthol with Vanadium Oxytrichloride.—Into the apparatus described under the general reaction procedure was placed 2 g (13 mmol) of 1-naphthol and 50 ml of dry benzene. The system was purged with nitrogen and 1 ml (10.5 mmol) of vanadium oxytrichloride was added. Vigorous evolution of hydrogen chloride and formation of dark residue followed. After the mixture was stirred for 15 min, 50 ml of sulfuric acid was added. The acidic layer turned blue, and a white crystalline residue settled out. This residue was filtered and dried to yield 0.92 g (56%) of 4,4′-dihydroxybinaphthyl, mp 297–229° (lit.[10] mp 300°).

Reaction of 1-Naphthol with Vanadium Tetrachloride.—Into the apparatus described in the general reaction procedure was placed 5.6 g (40 mmol) of 1-naphthol and 100 ml of dry benzene. After the apparatus was purged with nitrogen, the stirring was started and 40 mmol of vanadium tetrachloride in 14 ml of carbon tetrachloride was added. Vigorous evolution of hydrogen chloride was accompanied by the formation of dark precipitate. After 1 hr of stirring, the reaction mixture was decomposed with 50 ml of 1 *N* sulfuric acid. The residue was filtered, washed with water, and crystallized from alcohol to yield 2.3 g (40%) of 4,4′-binaphthol, mp 295–298° (lit.[10] mp 300°).

Determination of Hydrogen Chloride Yield in the Reaction of Phenol with Vanadium Tetrachloride.—Phenol (40 mmol) and vanadium tetrachloride (40 mmol) were allowed to react following the general procedure. A trap containing 200 ml of distilled water was connected to the flask to capture the hydrogen chloride evolved during the reaction. After the reaction was complete, nitrogen was bubbled through the reaction mixture for 1.5 hr to sweep the remaining hydrogen chloride into the water trap. The contents of the trap were titrated with 44.5 ml of 1.051 *N* sodium hydroxide to the phenophthalein end point. The reaction yielded 46.77 mequiv of hydrogen chloride (HCl/VCl_4, 1.2, and HCl/phenol, 1.2).

The reaction mixture was hydrolyzed with 50 ml of 1 *N* sulfuric acid and *p,p′*-diphenol was separated. The yield of *p,p′*-diphenol after washing with carbon tetrachloride was 1.4 g (38%).

The same procedure was used for the remaining experiments in Table II.

Registry No.—Vanadium tetrachloride, 7632-51-1; vanadium oxytrichloride, 7727-18-6; N,N,N′,N′-tetramethylbenzidine, 366-29-0.

(9) In one experiment, this residue was removed by vacuum filtration under nitrogen. *Anal.* Calcd: C, 31.33; H, 2.40; Cl, 20.83; O, 7.37.

(10) Handbook of Chemistry and Physics, C. D. Hodgman, R. C. Weast and S. M. Selby, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1959.

Formation of Cyclopropyl Ring by Action of Sodium Amide on *exo*-Methyleneammonium Ions Obtained from Rearrangement of Certain 2,6-Dimethylbenzyltrimethylammonium Ions[1]

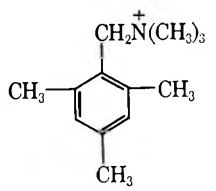
HAMAO WATANABE, FRANK N. JONES, AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina 27706

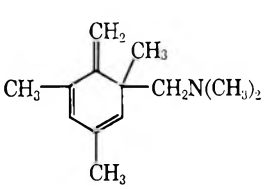
Received December 19, 1968

Reinvestigation (by nmr) of the structure of the product produced in the *ortho*-substitution rearrangement of the 2,4,6-trimethylbenzyltrimethylammonium ion by sodium amide in liquid ammonia, followed by two more such rearrangements of the methiodides of resulting *exo*-methyleneamines, has revealed that a cyclopropyl ring was introduced into the molecule. Similarly, two such rearrangements starting with the 2,3,5,6-tetramethylbenzyltrimethylammonium ion afforded an *exo*-methyleneamine having a cyclopropyl ring. Side reactions were observed in the latter case. Possible mechanisms are suggested.

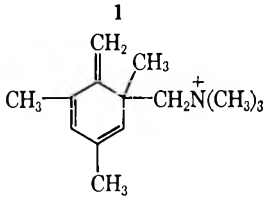
It has previously been shown that the 2,4,6-trimethylbenzyltrimethylammonium ion (**1**) can be rearranged by sodium amide in liquid ammonia to form the *exo*-methyleneamine **2**[2] and that **2** can be converted through the methiodide **3** into another *exo*-methyleneamine **4**[3] by further treatment with this reagent. However, the methiodide **5**, prepared from **4**, was converted by this reagent into an unknown alicyclic amine that was tentatively assigned structure **6**.[3]



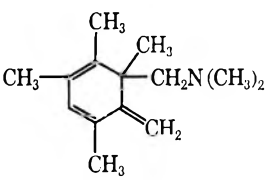
1



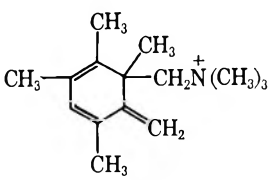
2



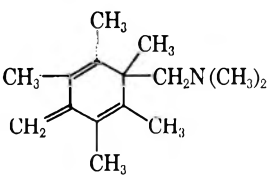
3



4



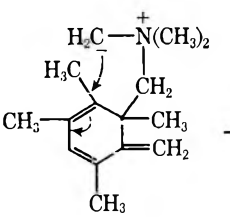
5



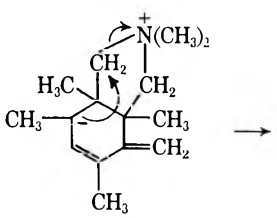
6

We have now obtained evidence that this last product is the *exo*-methyleneamine **9** having a cyclopropyl group. A possible mechanism for the introduction of the cyclopropyl group would involve addition of ylide **7** across the olefinic bond to form the resonance stabilized anion **8**, which undergoes an intramolecular displacement. Dreiding models indicate that ylide **7** can readily achieve a conformation favorable for such a mechanism. The last two steps might occur so rapidly that the mechanism is essentially concerted.

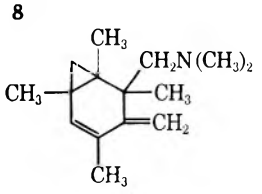
Structure **9** containing a cyclopropyl group was supported by analysis and by nmr, ir, and uv spectra. The nmr spectrum of **9** clearly showed an AB pattern at high field arising from the two cyclopropyl hydrogens. Other features of the spectrum were consistent with



7



8



9

structure **9**. Significantly, this *exo*-methyleneamine structure, which has only two conjugated double bonds, is in agreement with the earlier reported[3] failure of this compound to undergo rearomatization on heating at 150° or on treatment with dilute hydrochloric acid, conditions that effect rearomatization of *exo*-methyleneamines having three conjugated double bonds such as **2** and **4**.

Similarly, methiodide **11**, prepared from tertiary amine **10**, was converted into an *exo*-methyleneamine having a cyclopropyl group by only two rearrangements. Thus, **11** underwent rearrangement with sodium amide in liquid ammonia to form *exo*-methyleneamine **12**, most of which was converted through its methiodide **13** into the cyclopropyl derivative **14**. However, part of **12** evidently underwent isomerization to form *exo*-methyleneamine **15** (see below), and some of **15** may have been converted through its methiodide **16** into the cyclopropyl derivative **17** (Scheme I).

Cyclopropyl derivative **17** was not isolated but olefin **23**, which must have arisen through *exo*-methyleneamine **15**, was obtained along with olefin **20** as by-products when crude *exo*-methyleneamine **12** was treated with methyl iodide followed by alkali amide in liquid ammonia to form cyclopropyl derivative **14** (see Schemes I and II).

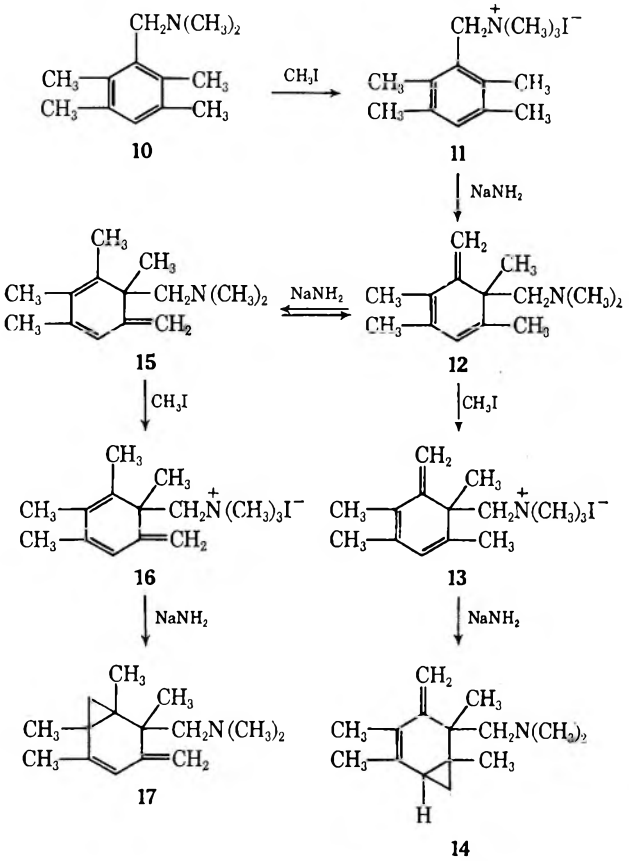
Although the cyclopropyl derivative **14** was obtained contaminated with small amounts of olefins **20** and **23**, **14** was isolated in the essentially pure condition by vpc; its structure was supported by analysis and absorption spectra. In contrast to the nmr spectrum of **9** which showed an AB system for the cyclopropyl protons, the nmr spectrum of **14** showed an ABC system. The nmr spectrum of **14** at 220 MHz showed clearly separated

(1) Supported by Army Research Office (Durham).

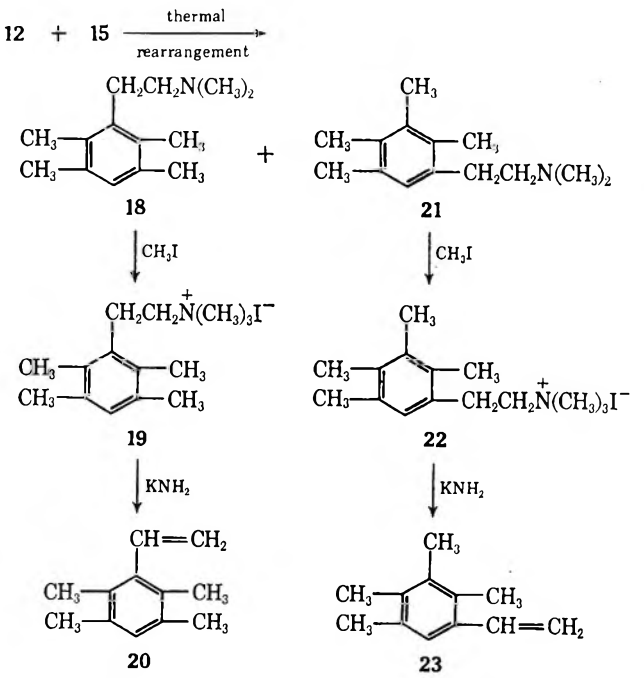
(2) C. R. Hauser and D. N. Van Eenam, *J. Amer. Chem. Soc.*, **79**, 5512 (1957).

(3) C. R. Hauser and D. N. Van Eenam, *ibid.*, **79**, 6280 (1957).

SCHEME I



SCHEME II

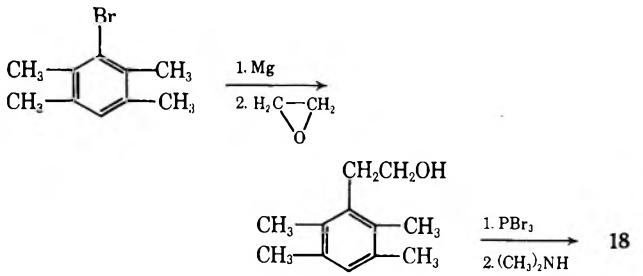


signals at high field arising from the three cyclopropyl hydrogens. Other features of the spectrum were consistent with structure **14**.

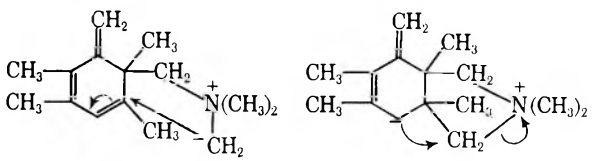
Like the cyclopropyl derivative **9** obtained from the mesityl methiodide **5** (see above), the cyclopropyl derivative **14** was found to be relatively stable toward heat and acid. Thus, **14** was recovered after distillation, after heating at 250° (vpc conditions), after standing at room temperature for more than 4 months, and after treatment with dilute hydrochloric acid.

The rearomatization of *exo*-methyleneamine **12** to form β-arylethylamine **18** was readily effected at 150–170° (see Scheme II). Although distilled *exo*-methyleneamine **12** was used in this thermal rearrangement, it was evidently contaminated with the isomeric amine **15**, since some of the β-arylethylamine **21** also appeared to be produced. Thus, treatment of the product with methyl iodide, followed by potassium amide, afforded olefins **20** and **23** in the ratio of about 4:1 (by vpc). The β-arylethylamine **18** was independently synthesized from bromodurene (Scheme III), and converted into pure olefin **20** through the methiodide **19**.

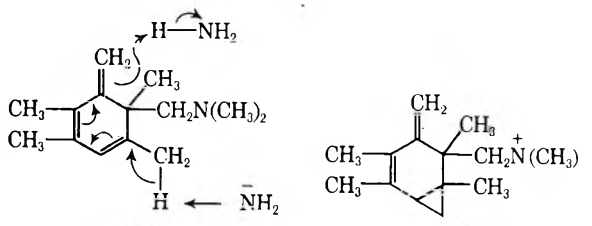
SCHEME III



The mechanism of the rearrangement of methiodide **13** to form the cyclopropyl derivative **14** (see Scheme I) may be indicated by **24** and **25**. Consideration of molecular models indicated that this mechanism is possible.



The isomerization of *exo*-methyleneamine **12** to form the isomeric *exo*-methyleneamine **15** (see Scheme I) presumably involves the amide ion catalyzed mechanism indicated in **26**. Incidentally, *exo*-methyleneamine **2** appears incapable of undergoing such a base-catalyzed isomerization and, although *exo*-methyleneamine **4** may isomerize, the process would lead only to regeneration of **4**.



The cyclopropylamine **14** was converted into its methiodide **27** but further treatment of this product with sodium amide failed to afford an isolable compound.

It should be mentioned that the present type of rearrangement of quaternary ammonium ions involving introduction of a cyclopropyl group into the molecule appears to be unprecedented in the literature. Studies are in progress on simpler models of this type of rearrangment.

Experimental Section[4]

Rearrangement of Methiodide 1 to Form *exo*-Methyleneamine 2. Conversion into Methiodide 3.—Rearrangement[2] of 1 was effected with $NaNH_2$ in liquid ammonia[5,6] to give 6-methylene-1,3,5-trimethyl-1-dimethylaminomethylcyclohexadiene-2,4 (**2**, 44%): bp 50–52° (0.45 mm); $n^{25}D$ 1.5120; uv λ_{max} 314 mμ (log ε 3.8); ir (neat) 3105 (C=CH_2), 1690, 1600 and 1580 cm^{-1} (C=C); nmr 5.65 (broad s, 1.0 H, C_4-H), 5.40 (broad s, 1.1 H, C_2-H), 5.22 (broad s, 1.0 H) and 5.02 (d, 0.9 H, J = 2.0 Hz, C=CH_2), 2.40 and 2.24 (AB pattern, 2.4 H, J = 13.2 Hz, CH_2N), 2.18 (s, 6.0 H, NCH_3), 1.89 (d, 2.8 H, J = 1.0 Hz, C_5-CH_3), 1.74 (d, 2.8 H, J = 1.7 Hz, C_3-CH_3), and 1.09 ppm (s, 2.7 H, C_1-CH_3).

Anal. Calcd for $C_{13}H_{21}N$: N, 7.32. Found: N, 7.29.

Methylation[3] of *exo*-methyleneamine **2** was effected with methyl iodide in acetonitrile to give *exo*-methyleneamine methiodide **3** (90%): mp 153–155° dec; ir (KBr) 3080 (C=CH_2), 1660 and 1570 cm^{-1} (C=C).

Rearrangement of *exo*-Methyleneamine Methiodide 3 to Form *exo*-Methyleneamine 4. Conversion into Methiodide 5.—Rearrangement[3] of **3** was effected with $NaNH_2$ in liquid ammonia[5,6] to afford 6-methylene-1,2,3,5-tetramethyl-1-dimethylaminomethylcyclohexadiene-2,4 (**4**, 62%): bp 65–67° (0.43–0.46 mm); $n^{25}D$ 1.5237; uv λ_{max} 319 mμ (log ε 4.0) (calcd λ_{max} 318 mμ); ir (neat) 3110 (C=CH_2), 1660, 1590 and 1570 cm^{-1} (C=C); nmr 5.63 (s, 1.0 H, C_4-H), 5.16 (s, 1.0 H) and 5.03 (d, 1.0 H, J = 2.0 Hz, C=CH_2), 2.55 and 2.25 (AB pattern, 2.1 H, J = 12.9 Hz, CH_2N), 2.13 (s, 5.9 H, NCH_3), 1.86 (s, C_5-CH_3) and 1.73 (s, C_2-CH_3 and C_3-CH_3, 9.0 H), and 1.13 ppm (s, 2.9 H, C_1-CH_3).

Anal. Calcd for $C_{14}H_{23}N$: N, 6.82. Found: N, 6.79.

Also, there was obtained from the above distillation β-isodurylethyldimethylamine (thermal isomerization product, 9%): bp 87–89° (0.36 mm); $n^{25}D$ 1.5180.

Anal. Calcd for $C_{14}H_{23}N$: N, 6.82. Found: N, 7.14.

This β-arylethylamine was evidently produced when a sample of *exo*-methyleneamine **4** was subjected to vpc at 270°, since the retention time observed was that of the aromatic compound.

Methylation[3] of *exo*-methyleneamine **4** was effected with methyl iodide in acetonitrile to give methiodide **5** (94%): mp 182–183° dec and 181–182° dec (recrystallized from acetonitrile–ether); ir (KBr) 3095 (C=CH_2), 1785, 1710, 1650, and 1570 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{25}NI$: C, 50.23; H, 7.28; N, 4.05. Found: C, 50.49; H, 7.68; N, 3.92.

Rearrangement of *exo*-Methyleneamine Methiodide 5 to Form *exo*-Methylene Bicyclic Amine 9.—To a stirred suspension of 0.255 mol of $NaNH_2$ in 300 ml of liquid ammonia[5,6] was added, during 5 min, 26.10 g of finely powdered *exo*-methyleneamine methiodide **5**. After stirring for 1 hr (color changed from deep purple-red to deep purple), the reaction mixture was decomposed with 10 g of NH_4Cl and then worked up as described previously.[3] The oily product (7.88 g) was distilled to give, after a small amount of forerun (0.30 g), 4.84 g (30%) of 3-methylene-1,2,4,6-tetramethyl-2-dimethylaminomethylbicyclo[4.1.0]heptene-4 (**9**): bp 71–72° (0.45 mm); $n^{25}D$ 1.5115; uv λ_{max} 257 mμ (log ε 4.0); ir (neat) 3113 (C=CH_2), 3060 (cyclopropylmethylene), 1760, 1665, 1640 and 1600 cm^{-1} (C=C); nmr 5.70 (broad s, 1.0 H, C_5-H), 5.03 (m, 2.1 H, C=CH_2), 2.75 and 2.55 (AB pattern, 2.2 H, J = 14.8 Hz, CH_2N), 2.35 (s, 6.0 H, NCH_3), 1.74 (d, 2.9 H, J = 1.3 Hz, C_4-CH_3), 1.19 (s, 6.0, H, C_1-CH_3 and C_6-CH_3), 0.93 (s, 3.0 H, C_2-CH_3), and 0.79 and 0.47 ppm (AB pattern, 2.0 H, J = 3.7 Hz, cyclopropyl methylene); the nmr spectrum was unchanged after the solution had stood at room temperature for 3 days.

Anal. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.39. Found: C, 81.90; H, 11.26; N, 6.52.

2,3,5,6-Tetramethylbenzyldimethylamine (10). Conversion into Methiodide 11.—Chloromethylation of durene (161 g) was effected as usual with aqueous formaldehyde, glacial acetic acid, and concentrated HCl. The crude chloromethydurene was added to a cold solution of dimethylamine (110 g) in acetonitrile (800 ml). After stirring for 3 hr at room temperature, the solvent was evaporated (steam bath) under reduced pressure. The residue was stirred with 400 ml of 20% NaOH. The liberated amine was taken up in benzene and converted into its hydrochloride salt with 500 ml of cold 10% HCl. The amine was again liberated with 300 ml of 20% NaOH and again taken up in benzene. The benzene solution was dried (Na_2CO_3) and fractionated to give 189.0 g (82%) of amine **10**: bp 135° (14 mm); nmr 6.88 (s, 0.9 H, C_4-H), 3.43 (s, 2.0 H, CH_2N), and 2.21 ppm (m, 18.0 H, C_2-CH_3, C_3-CH_3, C_5-CH_3, C_6-CH_3, and N-CH_3).

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.63; H, 11.42; N, 7.03.

Methylation of benzylamine **10** (186 g) was effected with methyl iodide (207 g) in acetonitrile (600 ml) to give, on stirring with anhydrous ether (1.3 l), 322.6 g (100%) of methiodide **11** as crystalline powder, mp 233–236° dec; recrystallization from dry acetonitrile afforded needles, mp 228° (darkened), 234–236° dec; ir (KBr) 3005 (aromatic C-H) and 870 cm^{-1} (pentasubstituted benzene ring).

Anal. Calcd for $C_{14}H_{24}NI$: C, 50.45; H, 7.26; N, 4.20. Found (before recrystallization): C, 50.34; H, 7.42; N, 4.07. Found (after recrystallization): C, 50.54; H, 7.40; N, 4.05.

Rearrangement of Methiodide 11 to Form *exo*-Methyleneamine 12.—To a stirred suspension of 0.45 mol of $NaNH_2$ in 500 ml of liquid ammonia[5,6] was added, during 5 min, 50.0 g (0.15 mol) of the methiodide **11** through Gooch tubing from an erlenmeyer flask (under anhydrous condition). After 2 hr (gray color changed to deep maroon), the reaction mixture was decomposed with 25 g of NH_4Cl. Anhydrous ether[7] (300 ml) was added dropwise while the liquid ammonia was evaporated on the steam bath. As soon as the ether began to reflux the reaction mixture was cooled and filtered. The solvent was removed at about 40° under reduced pressure, the last traces being removed *in vacuo* at 40°, to give 29.55 g (96% calculated as *exo*-methyleneamine **12**) of crude product (faintly yellow oil), $n^{25}D$ 1.5344. The uv and ir spectra of this crude product were almost identical with those of pure *exo*-methyleneamine **12** (see below).

Distillation of 10 g of the crude product under nitrogen through a Vigreux column gave 3.85 g (39%) of 6-methylene-1,2,4,5-tetramethyl-1-dimethylaminomethylcyclohexadiene-2,4 (**12**): bp 65–68° (0.16–0.20 mm); $n^{25}D$ 1.5259; uv λ_{max} 313[8] mμ (log ε 3.7) and 253[9] mμ (log ε 3.7); ir (neat) 3100 (C=CH_2), 1660, 1595 (sh), 1585 and 1565 cm^{-1} (sh) (C=C); nmr 5.65 (broad s, 0.9 H, C_3-H), 5.12 (s) and 4.97 (s) (1.9 H, C=CH_2), 2.53 and 2.23 (AB pattern, 2.3 H, J = 21.8 Hz, CH_2N), 3.82 (s, 6.0 H, NCH_3), 1.83 (s, 9.0 H, C_2-CH_3, C_4-CH_3 and C_5-CH_3), and 1.18 ppm (s, 2.7 H, C_1-CH_3).

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.79; H, 11.39; N, 6.72.

Also, there was obtained from the above distillation 3.17 g (32%) of β-arylethylamine **18** (contaminated with some of isomeric amine **21**), bp 82–84° (0.12–0.15 mm), $n^{25}D$ 1.5179, and 2.69 g of light brown residue. The amine **18** was identified by vpc (one peak having shoulder for **21**) and by ir and nmr spectra which were almost identical with those of **18** obtained by thermal isomerization of *exo*-methyleneamine **12** (see below).

Hydrolysis of *exo*-methyleneamine **12** (1.23 g) occurred rapidly on adding it to 30 ml of 2 *N* HCl at 0°. After stirring for 1.5 hr, the precipitate was collected, washed with water, and dried in air to give 0.67 g (75%) of pentamethylbenzene, mp 51–52°; the ir spectrum was identical with that of an authentic sample. The mixture melting point was not depressed.

Conversion of Crude *exo*-Methyleneamine 12 into Methiodide 13.—To a stirred solution of 29.25 g (0.142 mol) of freshly prepared (but not distilled) *exo*-methyleneamine **12** (containing some of *exo*-methyleneamine **15**) in 150 ml of anhydrous acetone was added, under nitrogen, 30.4 g (0.214 mol) of methyl iodide. After

(4) Melting and boiling points are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and by M-H-W Laboratories, Garden City, Mich. Uv spectra were produced on a Beckman DB-G spectrophotometer in 95% ethanol. Ir spectra were produced on a Perkin-Elmer Infracord, Models 137 and 237. Nmr spectra were obtained in deuteriochloroform with Varian A-60 and superconducting 220-MHz spectrometers and signals are reported in δ units downfield from internal tetramethylsilane standard. Vpc were carried out on F & M Model 500 with a 15-ft column of silicone gum rubber 30% on 60–80 mesh Chromosorb W at 250–270° and 120–200 ml/min of helium.

(5) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(6) Commercial anhydrous liquid ammonia was distilled and used immediately.

(7) Freshly distilled from calcium hydride after drying over calcium hydride and sodium borohydride.

(8) The intensity of this peak diminished on standing and completely disappeared after 11 days.

(9) This peak may be ascribed to a decomposition product.

1 hr, the precipitate was collected, washed with 30–50 ml of anhydrous acetone, and dried in a vacuum oven at 40° (for *ca.* 3 hr) to give 40.8 g (83%) of methiodide **13** (containing some of methiodide **16**): this white powder showed no sharp melting point, and darkened at 165–167°; mp 225–230° dec; ir (KBr) 3100 (C=CH_2), 1660 and 1585 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{26}NI$: C, 51.88; H, 7.55; N, 4.03. Found: C, 52.12; H, 7.63; N, 3.75.

Rearrangement of *exo*-Methlenecyclohexadieneamine Methiodide 13 to Form *exo*-Methylene Bicylic Amine 14.—To a stirred suspension of 0.152 mol of $NaNH_2$ in 300 ml of liquid ammonia[5,6] was added, during a few minutes, 40.7 g (0.117 mol) of *exo*-methyleneamine methiodide **13** (containing isomeric methiodide **16**). After 30 min, the deep pink-red suspension was treated with 15 g of NH_4Cl. The resulting mixture was worked up as described above for the rearrangement of methiodide **11** to give 10.04 g (39% calculated as bicyclic amine **14**) of a pale yellow liquid, $n^{25}D$ 1.5228, which was distilled under nitrogen through a Vigreux column to afford 0.62 g of forerun, bp 51–64° (0.2 mm), and 6.08 g (24%) of 3-methylene-1,2,4,5-tetramethyl-2-dimethylaminomethylbicyclo[4.1.0]heptene-4 (**14**) as colorless oil: bp 64–67° (0.20–0.22 mm); $n^{25}D$ 1.5139; uv λ_{max} 257 mμ (log ε 4.2); ir (neat) 3110 (C=CH_2), 3068 (cyclopropyl methylene), 1645 and 1610 cm^{-1} (C=C); nmr (220 MHz)[10] 4.96 (s or d, 2.0 H, C=CH_2), 2.76 and 2.56 (AB pattern, 2.0 H, J = 14 Hz, CH_2N), 2.39 (s, 6.0 H, NCH_3), 1.89 (s, 3.0 H, C_4-CH_3), 1.73 (s, 3.0 H, C_5-CH_3), 1.12 (s, 3.0 H, C_1-CH_3), 0.96 (s, 3.0 H, C_2-CH_3), and complex ABC pattern for cyclopropyl hydrogens at 0.90 (three lines, 1.0 H, J = 4 Hz), 0.76 (four lines, 1.0 H) and 0.63 ppm (three lines, 1.0 H).

Anal. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.39. Found: C, 82.42; H, 11.62; N, 6.24.

This sample of **14** was indicated by vpc to be 92–95% pure; the sample giving the main vpc peak was collected to give pure **14** ($n^{25}D$ 1.5133). The ir and nmr spectra were identical with those of the above sample; mass spectrum[11] (mol wt 219) *m/e* (intensity) 220 (1.5), 219 (8.3), 204 (2.4), 162 (2.4), 159 (3.4), 147 (6.8), 145 (2.0), 133 (2.0), 131 (2.0), 120 (2.9), 105 (3.4), 91 (4.0), 77 (2.9), 59 (6.3), 58 (100.0), 44 (2.4), 42 (7.4), 41 (4.4), 39 (2.4), 32 (2.0), 30 (4.4), and 28 (7.4).

Anal. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.39. Found: C, 82.23; H, 11.49; N, 6.12.

The forerun mentioned above was found by vpc to consist of vinyldurene **20** (40%), isomeric vinyl compound **23** (3%), and *exo*-methylene bicyclic amine **14** (45%); the two former vpc peaks were collected to give pure **20** and **23**. Pure compound **20**, mp and mmp 34.5–35.5°, gave ir and nmr spectra that were identical with those of independently synthesized **20** (see below).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.99; H, 10.18.

Pure compound **23** was a colorless liquid: ir (neat) 3090 (C=CH_2), 1625 and 1560 (C=C), and 876 cm^{-1} (pentasubstituted benzene ring); nmr 7.13 (s, C_6-H) and 7.02 (X portion of ABX pattern, vinyl αH, 2.2 H), 5.35 (center of AB portion of ABX pattern, J_{gem} = 1.9 Hz, 2.3 H, vinyl βH), and 2.25 ppm (d, 12.0 H, C_2-CH_3, C_3-CH_3, C_4-CH_3, and C_5-CH_3).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.64; H, 9.96.

When the rearrangement was repeated using 0.166 mol of $NaNH_2$ and 47.40 g (0.127 mol) of the crude methiodide **13** (containing isomeric methiodide **16**), there was obtained 11.10 g (37% calculated as bicyclic amine **14**), which was distilled to give 2.49 g of forerun, bp 54–70° (0.20–0.30 mm), and 5.76 g of **14** (19%, 85–87% pure by vpc), bp 71–74° (0.26–0.30 mm), $n^{25}D$ 1.5185; the ir and nmr spectra were identical with those of the above sample. The forerun was found by vpc to consist of vinyldurene **20** (50%), isomeric vinyl compound **23** (30%), and *exo*-methyleneamine **14** (20%); the two former peaks were collected and identified by ir and nmr.

Treatment of a pure sample of bicyclic amine **14** with dilute HCl and then with NaOH solution gave the recovered bicyclic amine **14**.

Thermal Isomerization of Crude *exo*-Methylamine 12 to Form β-Arylethyldimethylamines 18 and 21. Conversion into Olefins 20 and 23.—A 10-g sample of crude *exo*-methyleneamine **12**, bp 65–68° (0.16–0.20 mm), was heated at 150–170° (Wood's metal bath) for 5 hr. After cooling to room temperature, the mixture was filtered. The filtrate was distilled to give 6.10 g (61%) of β-durylethyldimethylamine (**18**), contaminated with some of its isomeric amine **21** (the vpc showed one peak for **18** with shoulder for **21**): bp 92.5–93° (0.30–0.35 mm); $n^{25}D$ 1.5170; ir (neat, strong peak) 3000–2700, 1460, 1045, 1037 and 860 cm^{-1}; nmr 6.84 (s, 0.8 H, aromatic) and 3.05–1.67 ppm (m, 22.0 H, others); also, the retention time in vpc was same as that of the above sample.

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.98; H, 11.54; N, 6.69.

Methylation of 4.30 g (0.02 mol) of a mixture of isomeric β-arylethylamines **18** and **21** was effected at 0° under nitrogen with 5.70 g (0.04 mol) of methyl iodide in 30 ml of dry acetonitrile. After 30 min, the reaction mixture was treated with 100 ml of anhydrous ether (stirred for 4 hr) to precipitate 7.00 g (96%) of a mixture of isomeric methiodides **19** and **22** (dried *in vacuo*): mp 267–269° dec; mmp with the authentic **19** 271–274° dec (mp 282–285°, see below).

Anal. Calcd for $C_{15}H_{26}NI$: C, 51.87; H, 7.55; N, 4.03. Found: C, 51.98; H, 7.44; N, 4.06.

β elimination was effected by adding 5.90 g (0.017 mol) of this mixture of methiodides **19** and **22** to 0.02 mol of KNH_2 in 150 ml of liquid ammonia.[5,6] After stirring for 30 min, the gray suspension was decomposed with 1 g of NH_4Cl, and the liquid ammonia was replaced by 200 ml of anhydrous ether.[7] The resulting mixture was worked up to give 2.11 g (78%) of a mixture of isomeric 2,3,5,6-tetramethylstyrene (**20**) and 2,3,4,5-tetramethylstyrene (**23**), bp 64–68° (0.40–0.45 mm); the composition of this mixture of **20** and **23** was 79 and 21%, respectively (by vpc).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.74; H, 10.09.

The two components of this mixture of isomeric olefins were separated by vpc, and samples were collected. Olefin **20** was identified by mp and mmp 34.5–35.5°, and by ir and nmr spectra which were identical with those of independently synthesized olefin **20** (see below).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.99; H, 10.18.

Olefin **23** was obtained as an oil; the ir and nmr spectra were identical with those of the above sample collected by vpc.

Independent Synthesis of β-Arylethylamine 18 and Olefin 20.—To a cold, stirred solution of the Grignard reagent prepared from 21.3 g (0.10 mol) of bromodurene and 2.56 g (0.105 g-atom) of magnesium turnings in 60 ml of tetrahydrofuran[12] (THF) was added, during 10 min, 9 g (0.20 mol) of ethylene oxide in 30 ml of THF.[12] After stirring for 6 hr at room temperature, the reaction mixture was hydrolyzed with 90 ml of 10% HCl and worked up to give, after recrystallization from methanol–water, 14.40 g (81%) of β-hydroxyethyldurene (bulky leaflets): mp 97–102 and 105–106° after another recrystallization; ir (KBr) 3260 (broad, OH), 1040 or 1020 (CO), and 860 cm^{-1} (pentasubstituted benzene ring); nmr 6.81 (s, 0.9 H, C_4-H), 3.90–2.83 (m of A_2B_2 type, 4.2 H, CH_2CH_2), 2.23 (s, 1.20 H, C_2-CH_3, C_3-CH_3, C_5-CH_3 and C_6-CH_3), and 2.16 ppm (s, 0.9 H, -OH).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.29; H, 10.34.

To 12.40 g (0.07 mol) of this alcohol (mp 97–102°) in 50 ml of anhydrous benzene was added 16.25 g (0.06 mol) of PBr_3 in 30 ml of anhydrous benzene (ice bath), and the mixture was stirred overnight at room temperature. The solution was concentrated and the residue was stirred with methanol to give, on slowly evaporating the solvent in a hood, 8.86 g (53%) of β-bromoethyldurene (bulky glittering leaflets), mp 54–56°, and 6.79 g (41%), mp 59–60°, after recrystallization from methanol: ir (KBr) 868 (pentasubstituted benzene ring) and 756 cm^{-1} (C-Br ?); nmr 6.96 (s, 0.8 H, C_4-H), 3.33 (broad s, 3.6 H, CH_2CH_2) and 2.22 ppm (s, 12.0 H, C_2-CH_3, C_3-CH_3, C_5-CH_3 and C_6-CH_3).

Anal. Calcd for $C_{12}H_{17}Br$: C, 59.76; H, 7.11. Found: C, 59.73; H, 7.08.

A solution of 14.5 g of this bromide (mp 54–60°) and 40 g of anhydrous dimethylamine in 70 ml of methanol was allowed to stand in the dark at room temperature for 10 days (stoppered flask). The solvent was evaporated, and the residual salt was treated with 90 ml of 40% NaOH. To an ethereal solution of the liberated amine was added 200 ml of 6 *N* HCl to precipitate

(10) We thank E. I. du Pont de Nemours and Co., Inc., for determination of this spectrum.

(11) We thank Dr. David Rosenthal for this determination, which was done at the Research Triangle Mass Spectrometry Center supported by Special Facility Grant No. FR-00330-01, National Institutes of Health.

(12) Freshly distilled from lithium aluminum hydride.

the amine salt. This salt was treated with NaOH to give 9.42 g (76%) of β-durylethyldimethylamine (18): bp 93° (0.26 mm) (solidified on cooling in an ice bath); $n^{25}D$ 1.5165; ir (neat, strong peak) 3000–2700, 1460, 1045, 1035, 1015, 864, and 857 cm^{-1}; nmr 6.82 (s, 0.8 H, aromatic) and 3.18–2.10 (m, 22.0 H, others).

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.82; H, 11.05; N, 6.90.

Methylation of 4.30 g (0.02 mol) of this amine was effected with 5.70 g (0.04 mol) of methyl iodide in acetonitrile to give 7.14 g (98%) of methiodide **19**, mp 282–285° dec.

Anal. Calcd for $C_{15}H_{26}NI$: C, 51.87; H, 7.55; N, 4.03. Found: C, 52.11; H, 7.44; N, 4.06.

β elimination was effected by adding 5.90 g (0.017 mol) of this methiodide **19** to 0.02 mol of KNH_2 in 150 ml of liquid ammonia[4,6] to give 2.11 g (78%) of 2,3,5,6-tetramethylstyrene (**20**): bp 51–52° (0.12–0.15 mm); mp 34.5–35.5°; ir (neat) 3080 ($C=CH_2$), 1625 and 1600 (C=C), and 866 cm^{-1} (pentasubstituted benzene ring); nmr 6.89 (s, C_4-H) and 6.74 (X portion of ABX pattern, vinyl αH, 2.1 H), 5.31 (center of AB portion of ABX pattern, J_{gem} = 2.4 Hz, vinyl βH), and 2.20 ppm (d, 12.0 H, C_2-CH_3, C_3-CH_3, C_5-CH_3 and C_6-CH_3).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.88; H, 10.02.

Conversion of *exo*-Methylene Bicyclic Amine 14 into Methiodide 27. Treatment with Sodium Amide.—Methylation of 3.92 g (0.0179 mol) of this amine was effected with 5.10 g (0.0358 mol) of methyl iodide in dry acetone (stirred for 3.5 hr) to give 2.10 g (33%) of methiodide **27** (white powder): mp 224–226° dec; ir (KBr) 3010 ($C=CH_2$), 3070 (cyclopropyl methylene), 1810 (C-H), 1635, 1600 and 1575 cm^{-1} (C=C).

Anal. Calcd for $C_{16}H_{28}NI$: N, 3.88. Found: N, 3.56.

To a stirred suspension of 0.0175 mol of $NaNH_2$ in 70 ml of liquid ammonia[5,6] was added 2.10 g (0.0058 mol) of methiodide **27**. After 3 hr, the deep orange-red mixture was decomposed with NH_4Cl, and the liquid ammonia was replaced by 50 ml of anhydrous ether.[7] The resulting mixture was worked up, but no isolable product was obtained in appreciable amount.

Registry No.—Sodium amide, 12125-45-0; **2**, 19990-87-5; **3**, 19990-88-6; **4**, 6968-88-3; β-isodurylethyldimethylamine, 5336-63-0; **5**, 19990-91-1; **9**, 19990-92-2; **10**, 19990-93-3; **11**, 19990-94-4; **12**, 19990-95-5; **13**, 19990-96-6; **14**, 19990-97-7; **18**, 19990-98-8; **19**, 19990-99-9; **20**, 2039-91-0; **21**, 19991-01-6; **22**, 19991-02-7; **23**, 3937-22-2; β-hydroxyethyldurene, 19991-04-9; β-bromoethyldurene, 19991-05-0; **27**, 19991-06-1.

Aminolyses of Sulfinic Acid Derivatives[1]

YUNN HUI CHIANG, JEROME S. LULOFF, AND EDGAR SCHIPPER[2]

Division of Central Research, Shulton, Inc., Clifton, New Jersey

Received September 25, 1968

A series of alkane- and arenesulfinamides was prepared from the corresponding sulfinyl chloride. Treatment of the chlorolysis product of dithiodiglycolic acid with morpholine produced 4-morpholinosulfinylacetomorpholide (**1**). Dimorpholide **1** was a stable, water-soluble, and slightly acidic substance. The infrared spectrum resembled that of the simple alkanesulfinamides in the region of 1500–650 cm^{-1}. However, between 3000 and 2500 cm^{-1} the spectrum exhibited a series of bands characteristic of amine salts. In addition, there were two strong bands at 1630 and 1610 cm^{-1} assignable to conjugated C=C stretching and C=O stretching vibrations. The ultraviolet spectrum of **1** exhibited one maximum at 273 mμ (ε 14,000) which did not shift in the presence of base. From a consideration of the spectral data and the saltlike physical properties of compound **1**, it appears that its structure is best represented by the betaine resonance hybrid **1a** ↔ **1b**. Under controlled conditions, oxidation of 3,3′-dithiodipropionic acid by chlorine led to 1,2-oxathiolan-5-one 2-oxide (**3**), which upon aminolysis with aromatic amines gave sulfonyl dipropionamides **5**. The structure of **3** was confirmed by molecular weight determinations (Rast method), saponification equivalent, alkaline permanganate oxidation, and elementary analysis. Mechanisms for the formation of **3** and its aminolysis products are presented.

In a search for agents capable of reconstituting reduced keratin, a process involving mild oxidation of thiol to disulfide groups, our attention turned to the little known class of sulfinamides $RSONR^1R^2$. Several years ago, Smith and Grasley[3] reported, as part of their work relating to antiradiation drugs, the oxidation of 2-aminoethanethiol to its disulfide in the presence of certain arenesulfinamides.

$$RSONR_2 + 2R'SH \longrightarrow R'SSR' + RSNR_2 + H_2O$$

While arenesulfinamides have been known for some time,[4] amides derived from alkanesulfinic acids became accessible only after a facile method for the synthesis of alkanesulfinyl chlorides had been discovered.[5] Douglass and Farah[6] reported the aminolysis of methanesulfinyl chloride with several aromatic amines, and Moriarty[7] more recently applied this method to the synthesis of a few N,N-dialkylalkanesulfinamides, the first members of this class of compounds.[8]

The sulfinamides prepared in our laboratories by amonolysis and aminolysis of a variety of arene- and alkanesulfinyl chlorides are listed in Table I. In general, the sulfinamides obtained were unpleasant smelling, colorless liquids, distillable at low pressures. They were soluble in most organic solvents; the lower molecular weight derivatives and those containing morpholine groups were unstable and discolorized gradually on exposure to air. The sulfinamides were rapidly oxidized by alkaline permanganate, but the corresponding sulfonamides expected as end products of the oxidation[6] could not be isolated. The infrared (ir) spectra of the sulfinamides showed strong absorptions at 1070 and 1010 cm^{-1} assignable to S=O stretching vibrations.[9]

(1) Presented at the 150th National Meeting of The American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) Ethicon, Inc., Somerville, N. J.

(3) W. T. Smith, Jr. and M. Grasley, Abstract, the 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962, p 36N.

(4) L. C. Raidord and S. E. Hazlet, *J. Amer. Chem. Soc.*, **57**, 2172 (1935).

(5) (a) I. B. Douglass and D. R. Poole, *J. Org. Chem.*, **22**, 536 (1957); (b) I. B. Douglass and B. S. Farah, *ibid.*, **23**, 330 (1958); (c) I. B. Douglass, B. S. Farah, and E. G. Thomas, *ibid.*, **26**, 1996 (1961); (d) I. B. Douglass and B. S. Farah, *Org. Syn.*, **40**, 62 (1960).

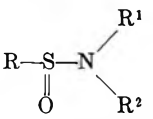
(6) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **23**, 805 (1958).

(7) R. M. Moriarty, *Tetrahedron Lett.*, No. 10509 (1964).

(8) The use of a number of N,N-dialkylsulfinamides as bird repellants without claiming or describing a method of preparation has been disclosed: L. D. Goodhue, R. P Louthan, and K. E. Cantrel, U. S. Patent 2,955,980 (1960).

(9) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958, pp 350–364.

TABLE I
SULFINAMIDES



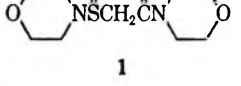
R	R¹	R²	% yield[a]	Bp (mm), °C	Empirical formula	Registry no.	Calcd, % C	H	N	S	Found, % C	H	N	S
CH_3	CH_3	CH_3	16	38 (1.2)	[b]	920-56-9								
CH_3	C_2H_5	C_2H_5	11	55 (1.8)	$C_5H_{13}NOS$	921-77-7	45.39	9.69	10.36	23.72	44.21	10.00	10.31	23.80
CH_3	$CH_2CH_2OCH_2CH_2$		42	81 (0.25)	$C_6H_{11}NO_2S$	13455-93-1	40.24	7.43	9.39	21.49	40.53	7.52	9.39	21.23
CH_3	H_3C CH_3 | | $CH_2CHOCHCH_2$		17	72 (0.1)	$C_7H_{15}NO_2S$	19955-33-0	47.42	8.53	7.90	18.09	47.68	8.50	7.70	17.94
CH_3	CH_3 | $CH_2CH_2NCH_2CH_2$		40	68 (0.08)	$C_6H_{14}N_2OS$	19955-34-1	44.41	8.70	17.27	19.77	44.43	8.66	16.88	193.8
C_2H_5	CH_3	CH_3	13	50 (4)	[b]	921-05-1								
C_2H_5	C_2H_5	C_2H_5	39	55 (1.3)	$C_8H_{15}NOS$	10408-13-6	48.28	10.13	9.39	21.49	48.25	10.34	9.20	21.18
C_2H_5	$CH_2CH_2OCH_2CH_2$		27	84 (0.1)	$C_6H_{13}NO_2S$	19955-37-4	44.14	8.03	8.58	19.65	44.37	8.38	8.40	19.30
$CH_3CH_2CH_2$	CH_3	CH_3	20	55 (1.1)	$C_6H_{13}NOS$	923-05-7	44.41	9.69	10.36	23.72	44.64	10.06	10.65	23.52
$CH_3CH_2CH_2$	C_2H_5	C_2H_5	73	60 (0.25)	$C_7H_{17}NOS$	19955-39-6	51.49	10.50	8.58	19.64	51.04	10.56	8.70	19.80
$CH_3CH_2CH_2$	$CH_2CH_2OCH_2CH_2$		80	88 (0.08)	$C_7H_{15}NO_2S$	19955-40-9	47.42	8.53	7.90	18.09	47.45	8.77	8.10	18.33
$(CH_3)_2CH$	H	H	9	64–65[c]	C_3H_9NOS	1955-41-0	33.62	8.46	13.07	29.29	33.62	8.70	13.10	29.71
$(CH_3)_2CH$	CH_3	CH_3	41	66 (6)	$C_5H_{13}NOS$	921-15-3	44.41	9.69	10.36	23.72	44.33	9.77	10.47	23.61
$(CH_3)_2CH$	C_2H_5	C_2H_5	50	60 (0.4)	$C_7H_{17}NOS$	19955-43-2	51.49	10.50	8.58	19.63	51.26	10.43	8.72	19.92
$(CH_3)_2CH$	$CH_2CH_2OCH_2CH_2$		38	80 (0.1)	$C_7H_{15}NO_2S$	19955-44-3	47.42	8.53	7.90	18.09	47.05	8.77	8.00	18.15
C_6H_5	CH_3	CH_3	43	73 (0.1)	$C_8H_{11}NOS$	5539-54-8	56.77	6.55	8.28	18.95	56.67	6.68	8.39	18.88
p-$NO_2C_6H_4$	$CH_2CH_2OCH_2CH_2$		19	128–130[d]	$C_{10}H_{12}N_2O_4S$	19955-46-5	46.86	4.72	10.93	12.51	47.10	4.60	11.08	12.36

[a] Yield is based on sulfinyl chloride. [b] R. M. Moriarty, *J. Org. Chem.*, **30**, 600 (1965). [c] Melting point; compound was recrystallized from ether. [d] Melting point; compound was recrystallized from an ethanol–methanol mixture.

In the primary amide, 2-propanesulfinamide, absorption occurred at 1040 and 1010 cm^{-1}, a shift indicative of hydrogen bonding;[10] strong association also was evident from the greatly shifted N—H stretching absorption at 3200 and 3100 cm^{-1}. In addition, the sulfinamides absorbed in the region of 700–660 cm^{-1} (C—S stretching[9] at 920–900 cm^{-1} [11]).

The oxidative power of the sulfinamides toward mercapto groups was determined semiempirically on ammonium and monoethanolamine thioglycolate reduced hair by the waving efficiency test of Kirby.[12] Of all of the compounds tested, only 2-propanesulfinamide showed promising oxidative properties. Since many of the compounds were not sufficiently soluble under the aqueous testing conditions, the incorporation of a solubilizing moiety became desirable and to this end the synthesis of a carboxyalkanesulfinamide was attempted.

Chlorination of dithiodiglycolic acid in the presence or absence of acetic acid followed by aminolysis with morpholine yielded the dimorpholide **1** instead of the desired carboxymethylsulfinamide.

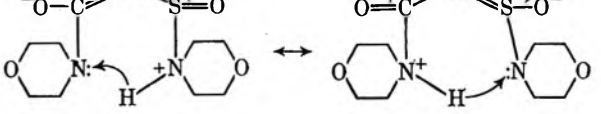


1

This finding was not unexpected in view of the report of Douglass and Farah[13] who isolated analogous diamides when they subjected 3-mercaptopropionic acid and 4,4′-dithiodibutyric acid to chlorolysis and subsequently treated the resulting intermediate with aniline.

The dimorpholide **1**, mp 189–190°, was a stable, water-soluble, and slightly acidic substance (pH 5.7 for a 1% aqueous solution). The compound readily decolorized bromine and alkaline permanganate but was not affected by treatment with neutral hydrogen peroxide. The ir spectrum resembled that of the simple alkanesulfinamides in the region of 1500–650 cm^{-1}. However, between 3000 and 2500 cm^{-1} the spectrum exhibited a series of bands characteristic of amine salts. In addition, there were two strong bands at 1630 and 1610 cm^{-1} assignable to conjugated C=C stretching and C=O stretching vibrations. The ultraviolet (uv) spectrum of **1** exhibited one maximum at 273 mμ (ε 14,000) which did not shift in the presence of base. The high absorbance at this wavelength is strongly reminiscent of the spectrum of the predominantly enolic acetylacetone [273 mμ (ε 10,000)].[14]

From a consideration of the spectral data and the saltlike physical properties of compound **1**, it appears that its structure is best represented by the betaine resonance hybrid **1a** ↔ **1b**; abstraction of a proton by base, it may be noted, does not alter the character of the chromophore in this representation.



1a **1b**

Attempts to extend the aminolysis of chlorosulfinylacetyl chloride to amines other than morpholine were unsuccessful. A variety of alkyl, aryl, and heterocyclic amines (including piperidine) were employed, but in every instance the reaction products consisted of dark oils or tars which could not be purified. The unique success achieved with morpholine can be rationalized on the basis of its high nucleophilic character which is

(10) E. D. Amstutz, I. M. Hunsberger, and J. J. Chessik, *J. Amer. Chem. Soc.*, **73**, 1220 (1951).

(11) The absorption around 900 cm^{-1} appears to be specific for sulfinamides since other tetravalent sulfur derivatives (sulfinic acids, sulfoxides, etc.) do not exhibit peaks in this region.

(12) D. H. Kirby, *Drug Cosmetic Ind.*, **80**, 314 (1957).

(13) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **26**, 351 (1961).

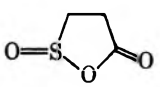
(14) M. J. Kamlet, "Organic Electronic Spectral Data," Vol. 1, Interscience Publishers, New York, N. Y., 1960, pp 60, 61.

coupled with a low basicity.[15] This combination of properties greatly favors bimolecular substitution over elimination reactions.[16] In the presence of more basic amines, however, the elimination reaction predominates which in the case of the postulated intermediate sulfinylacetyl chloride may give rise to a highly labile sulfine.[17]

Since the ability of the dimorpholide **1** to reconstitute disulfide bonds in reduced-hair keratin was equal to that of hydrogen peroxide,[12] it seemed desirable to examine similar diamides in the homologous series.

Chlorolysis of 3,3′-dithiodipropionic acid with 3 mol of chlorine, followed by reaction with *n*-butylamine gave the expected dibutyramide derivative, n-$C_4H_9NHC(=O)CH_2CH_2S(=O)NHC_4H_9$-$n$ (**2**).

During the chlorination step the formation of a precipitate was observed. When the reaction was terminated after a chlorine uptake of only 2 mol, the solid product could be obtained in its maximum yield. The material contained no chlorine, and elementary analysis, molecular weight determinations (Rast method), saponification equivalent, and alkaline permanganate oxidation according to the method of Allen[18] indicated that the hitherto-unknown anhydride of β-carboxyethanesulfinic acid, 1,2-oxathiolan-5-one 2-oxide (**3**), was at hand.



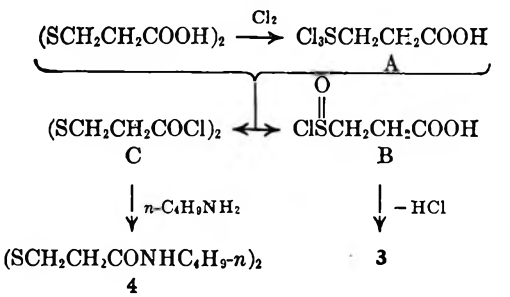
3

Compound **3** was insoluble in cold water, but it could be recrystallized from hot neutral or acidic aqueous solutions; it dissolved readily in base, and it could be recovered unchanged upon neutralization of its basic solution. The material could not be oxidized by hydrogen peroxide to the known 1,2-oxathiolan-5-one 2,2-dioxide.[19] The ir spectrum of **3** showed major bands at 1700 (C=O stretching), 1320 and 1240 (cyclic C—O stretching), and 1150 and 1110 cm^{-1} (S=O stretching).

The nmr spectrum of **3** had signals at τ 7.0 (d, 2 H), 6.6 (m, 1 H), and 6.1 (m, 1 H). Since chemically there are only two species of protons in **3**, the nonequivalence of one of the species is required by the spectrum. The chemical shift at τ 7.0, a doublet of doublets, can readily be assigned by analogy with succinic anhydride[20] to the protons adjacent to the carbonyl group. The nonequivalence of the geminal protons adjacent to the sulfinyl group is a further demonstration of tetravalent sulfur asymmetry.[21]

In addition to **3**, chlorolysis of 3,3-dithiodipropionic acid with 2 mol of chlorine gave rise to an oil which could not be distilled without decomposition. Reaction of the crude oil with butylamine resulted in the formation of N,N′-dibutyldithiodipropionamide (**4**), a compound obviously derived from dithiodipropionyl chloride. The formation of this acid chloride as by-product in the synthesis of **3** suggests the reaction mechanism shown in Scheme I.

SCHEME I



In this reaction sequence the starting material disproportionates in the presence of its primary chlorination product (A) according to the general scheme of Douglass, *et al.*,[5c] to yield compounds B and C. The stoichiometry of this reaction requires only 1.5 mol of chlorine/mol of starting material.

$$2(SCH_2CH_2COOH)_2 + 3Cl_2 \longrightarrow C + 2B + 2HCl$$

In passing it may be noted that the nature of the products isolated from the chlorolysis of 3,3-dithiodipropionic acid, with less than 3 mol of chlorine, favors an intermolecular solvolysis of intermediate A[22] rather than the intramolecular mechanism proposed by Douglass and Farah.[13]

Aminolysis of 1,2-oxathiolan-5-one 2-oxide (**3**) with aliphatic amines led to complex products which could not be identified, but the reaction with aniline and substituted anilines gave moderate yields of the symmetrical sulfones **5**. The structure of the unsubstituted dianilide **5** (Ar = C_6H_5) was proven by comparison with an authentic sample prepared from 3,3′-sulfonyldipropionic acid *via* the acid chloride. The unexpected formation of the sulfones by aminolysis of **3** can be rationalized tentatively as shown in Scheme II.

This scheme postulates—in analogy with the observation of Kharasch, *et al.*,[19] on the aminolysis of 1,2-oxathiolan-5-one 2,2-dioxide—a nucleophilic attack at C-5 resulting in the sulfinic acid intermediate D. Compounds of this type are known to be subject to facile base-catalyzed β eliminations involving expulsion

(15) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956).
(16) N. H. Cromwell and P. H. Hess, *ibid.*, **83**, 1237 (1961).
(17) W. A. Sheppard and J. Diekmann, *ibid.*, **86**, 1891 (1964).
(18) P. Allen, Jr., *J. Org. Chem.*, **7**, 23 (1942).
(19) M. S. Kharasch, T. H. Chao, and H. C. Brown, *J. Amer. Chem. Soc.*, **62**, 2393 (1940).
(20) N. S. Bhacca, B. P. Hollis, L. F. Johnson, and E. A. Pier, "N.M.R. Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963.
(21) (a) G. M. Whitesides, D. Holz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 2628 (1964); (b) J. G. Pritchard and P. C. Lauterbur, *ibid.*, **83**, 2105 (1961); (c) K. Mislow, A. L. Ternay, Jr., and J. T. Meillilo, *ibid.*, **85**, 2329 (1963); (d) R. M. Moriarty, *J. Org. Chem.* **30**, 600 (1965).

(22) The formation of the ultimate reaction product, 3-chlorosulfinylpropionyl chloride which arises when chlorine is used in excess (3 mol) may be explained by the following scheme.

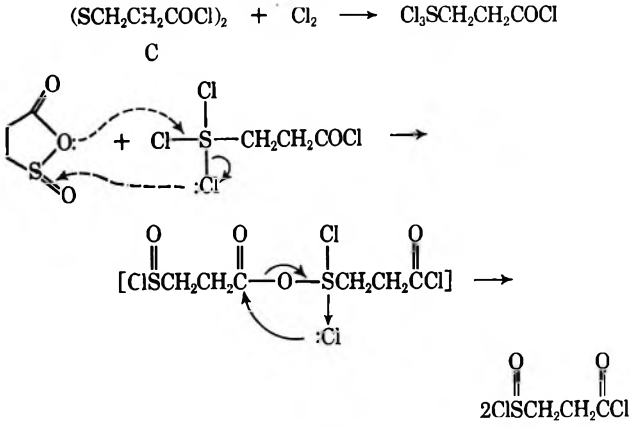
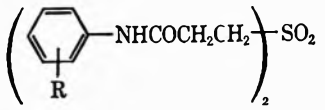


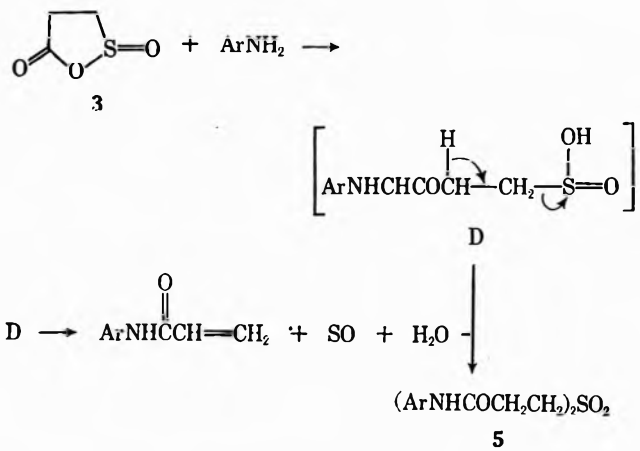
TABLE II

SULFONES



R	% yield	Mp, °C	Recrystn solvent	Empirical formula	Registry no.	Calcd, % C	H	N	S	Cl	Found, % C	H	N	S	Cl
H	8	246–247	EtOH	$C_{18}H_{20}N_2O_4S$	19955-47-6	59.98	5.59	7.77	8.90		59.82	5.55	7.75	8.97	
o-CH_3	12	255	EtOH	$C_{20}H_{24}N_2O_4S$	19955-48-7	61.83	6.23	7.21	8.26		61.95	6.45	7.14	7.83	
p-CH_3	20	271–272	EtOH	$C_{20}H_{24}N_2O_4S$	19955-49-8	61.83	6.23	7.21	8.26		61.65	6.25	7.33	8.15	
o-Cl	21	234–235	EtOH	$C_{18}H_{18}Cl_2N_2O_4S$	19955-50-1	50.35	4.23	6.53	7.47	16.52	50.55	4.36	6.53	7.35	16.42
p-Cl	6	290–291	Acetone–EtOH (2:3)	$C_{18}H_{18}Cl_2N_2O_4S$	19955-51-2	50.35	4.23	6.53	7.47	16.52	50.28	4.45	6.56	7.60	16.68
o-OCH_3	2	175–176	Acetone–hexane (1:3)	$C_{20}H_{24}N_2O_6S$	19955-52-3	57.13	5.75	6.66	7.63		57.24	5.78	6.87	7.75	

SCHEME II



of a sulfur fragment.[23] Combination of D with its β-elimination product (acrylanilide) then can be expected to lead to **5** in accordance with the well-known synthesis of sulfones by the addition of sulfinic acids to α,β-unsaturated species.[24]

Experimental Section[25]

Preparation of Sulfinamides. General Procedure.—To a stirred solution of 0.4 mol of an amine in 150 ml of methylene chloride, 0.2 mol of a sulfinyl chloride[5c,26] was added dropwise over a period of 1 hr. The reaction was run under a nitrogen atmosphere and at a temperature of −20 to −40° maintained by means of an acetone–Dry Ice bath. After complete addition, the reaction mixture was stirred for 1 hr at room temperature. The precipitate consisting of amine hydrochloride was filtered off and the solvent was removed from the filtrate by distillation. The reaction residue, in the case of a solid, was recrystallized from an appropriate solvent; liquid sulfinamides were distilled at reduced pressure and at temperatures not exceeding 90°. At higher distillation temperatures extensive decomposition took place.

The individual sulfinamides prepared by the above method are listed in Table I. The ir spectrum gave signals at 1070–1010 (S=O) and 700–660 cm^{-1} (C—S).

4-Morpholinosulfinylacetomorpholide (1).—To a stirred suspension of 45.5 g (0.25 mol) of dithiodiglycolic acid in 200 ml of methylene chloride was added over a period of 1 hr 36.0 g (0.5 mol) of chlorine gas while the reaction temperature was maintained at 0–10° by means of an acetone–Dry Ice bath. Gradually all suspended material went into solution. After completed addition, the solution was stirred at room temperature and subsequently at 40° to remove all of the hydrogen chloride formed in the reaction. The solvent was removed under reduced pressure to leave an oily residue of crude chlorosulfinylacetyl chloride which was used as such in the following step.

A solution of 174 g (2.0 mol) of morpholine in 300 ml of methylene chloride was allowed to react with a solution of 80.5 g (0.5 mol) of the above crude chlorosulfinylacetyl chloride in 250 ml of methylene chloride according to the general procedure for the preparation of sulfinamides. After complete reaction, the solution was condensed to a volume of 250 ml. The solid, consisting mainly of morpholine hydrochloride, was filtered off and the filtrate was condensed further to a volume of 50 ml. The resulting precipitate was collected by filtration and recrystallized several times from 95% ethanol: yield 57 g (54%), mp 189–190°.

Anal. Calcd for $C_{10}H_{18}N_2O_4S$: C, 45.78; H, 6.91; N, 10.68 S, 12.23. Found: C, 45.68; H, 7.07; N, 10.55; S, 12.45.

Reactions of the chlorosulfinylacetyl chloride with aniline, piperidine, diethylamine, and N-methyl piperazine failed to give identifiable products.

N-*n*-Butyl-3-*n*-butylaminosulfinylpropionamide (2).—A solution containing 73 g (1 mol) of *n*-butylamine in 250 ml of methylene chloride was treated with a solution of 40 g (0.23 mol) of crude 3-chlorosulfinylpropionyl chloride[13] in 250 ml of methylene chloride according to the general procedure for the preparation of sulfinamides. After removal of the reaction solvent the semisolid residue was triturated with 100 ml of ethyl acetate and the solid consisting of *n*-butylamine hydrochloride was filtered off. The filtrate was washed several times with water and dried. After removal of the solvent there remained a colorless solid which was recrystallized from ethyl acetate: yield 13 g (20%), mp 82–84°.

Anal. Calcd for $C_{11}H_{24}N_2O_2S$: C, 53.19; H, 9.74; N, 11.28; S, 12.91. Found: C, 53.09; H, 9.73; N, 11.36; S, 12.98.

1,2-Oxathiolan-5-one 2-Oxide (3).—To a stirred solution containing 105 g (0.5 mol) of dithiodipropionic acid in 200 ml of methylene chloride was added 71 g (1.0 mol) of chlorine gas over a period of 2 hr. The reaction temperature was maintained at −20 to −40° and, after complete addition, the reaction mixture was allowed to warm to room temperature. The solution was filtered and the filtrate was worked up as described below. The precipitate was recrystallized several times from ethyl acetate: yield 28.5 g (48%), mp 148–150°.

Anal. Calcd for $C_3H_4O_3S$: C, 29.99; H, 3.36; S, 26.70; mol wt, 120. Found: C, 30.02; H, 3.57; S, 26.73; mol wt (Rast), 120.

N,N′-Dibutyldithiodipropionamide (4).—The filtrate from the preceding reaction was condensed under reduced pressure to leave an oily residue which was dissolved in 100 ml of methylene chloride. This solution was used for the acylation of 73 g (1 mol) of *n*-butylamine according to the conditions described for the preparation of compound **2**. After complete reaction, the reaction mixture was washed several times with water and dried. The solvent was removed under reduced pressure. The residue, a colorless solid, was recrystallized from ethyl acetate: yield 3.3 g (2%), mp 130–131°.

Anal. Calcd for $C_{14}H_{28}N_2O_2S_2$: C, 52.46; H, 8.80; N, 8.74; S, 20.01. Found: C, 52.33; H, 8.61, N, 8.53; S, 20.48.

(23) (a) A. T. Kader and C. J. M. Stirling, *J. Chem. Soc.*, 3686 (1962); (b) D. S. Campbell and C. J. M. Stirling, *ibid.*, 5869 (1964); (c) F. Weygand and W. Steglich, *Chem. Ber.*, **98**, 487 (1965); (d) T. J. Wallace, H. Pobiner, J. E. Hofmann, and A. Schriesheim, *J. Chem. Soc.*, 1271 (1965).

(24) E. Schjanberg, *Ber.*, **76**, 287 (1943).

(25) All melting points were measured in a Thomas–Hoover apparatus. Melting and boiling points are uncorrected. Ir curves were obtained on a Perkin-Elmer Model 21 and nmr measurements were made on a Varian A-60.

(26) I. B. Douglass, K. R. Brewer, and F. T. Martin, *J. Amer. Chem. Soc.*, **74**, 5770 (1952).

Aminolysis of 3. Preparation of Sulfones 5.—A mixture of 0.03 mol of **3** and 0.15 mol of an arylamine was heated for 12 hr under a nitrogen atmosphere at 130–160°. The reaction product was washed with consecutive portions of 10% hydrochloric acid and water. The washed material was dissolved in 100 ml of 95% ethanol; the solution was charcoaled and condensed to one-half volume. The product was filtered off and recrystallized from an appropriate solvent.

The individual sulfones prepared by this method are listed in Table II.

3,3′-Sulfonyldipropionanilide (5, Ar = C_6H_5).—A solution consisting of 9.9 g (0.05 mol) of 3,3′-sulfonyldipropionic acid,[27] 75 ml of thionyl chloride, and 100 ml of chloroform was refluxed for 48 hr. The solvent and excess thionyl chloride were removed by distillation and the residue was dissolved in 150 ml of methylene chloride. This solution was added dropwise to a stirred solution of 18.6 g (0.2 mol) of aniline in 150 ml of methylene chloride. Stirring at room temperature was continued for 2 hr after complete addition. The solid was filtered off and extracted several times with hot water. The water-insoluble material was recrystallized from ethanol: yield 7.4 g (41%), mp 246–247°.

The reaction product was identical (melting point, mixture melting point, and ir spectrum) with the material obtained from the aminolysis of 1,2-oxathiolan-5-one 2-oxide **3** with aniline.

(27) H. S. Schultz, H. B. Freyermuth, and S. R. Buc, *J. Org. Chem.*, **28**, 1140 (1963).

Registry No.—**1**, 10408-21-6; **2**, 19955-27-2; **3**, 19955-28-3; **4**, 927-42-4.

Preparation and Reactions of Diazo Ketones. V.[1] Normal and Abnormal Products from Thermal Wolff Rearrangement of 9-Phenylfluorene-9-carbonyldiazomethane

ALFRED L. WILDS, RICHARD L. VON TREBRA, AND NEIL F. WOOLSEY

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received August 26, 1968

As one test of the role of steric factors in leading to abnormal thermal Wolff rearrangement of the diazomethyl ketone **1** from triphenylacetic acid, diazomethyl ketone **5** was prepared from 9-phenylfluorene-9-carboxylic acid (**4a**). Thermal Wolff rearrangement of **5** in 1-hexanol and N-ethylmorpholine gave 50–55% of normal product **6** as well as 35–40% of abnormal product **7**. Decarboxylation of acid **7a** gave 1-methyl-9-phenylfluorene (**9**), which was synthesized from 1-methyl-9-fluorenone (**11**). Nmr spectra for these compounds provide confirmatory proof of structures. The formation of considerable normal product **6** in the 9-phenylfluorene example **5**, compared with none in the triphenylmethane case **1**, supports the view that steric factors are important in impeding normal rearrangement of the latter.

Some years ago in this laboratory, as a result of our interest in using the Arndt–Eistert synthesis of homologous acids in certain synthetic sequences, we undertook a series of investigations aimed at widening the scope of the method, improving the reliability of the experimental procedures, and throwing further light on the mechanisms of the reactions. Wilds and Meader[1a] reported solutions for two of the problems involved, the first concerning the preparation of diazo ketones from acid chlorides and higher diazohydrocarbons,[2,3] and the second an improved and more general method for rearranging diazo ketones to derivatives of the homologous acids.

With these problems clarified, we turned to a study of the synthetic and mechanistic consequences of increasing the steric requirement of the acid chloride on the formation of the diazo ketone, and also on the Wolff rearrangement of the latter. It was known that mesitoyl chloride failed to give a diazo ketone with diazomethane.[4,5] This diazo ketone prepared in another way, however, underwent normal rearrangement to the higher acid, as did 2,4,6-triisopropylbenzoyldiazomethane.[6] Consequently it is clear that the steric requirements of the two steps in the Arndt–Eistert sequence are quite different.

Significant results were obtained by Van Den Berghe[5] in the series *n*-butyryl, isobutyryl, and trimethylacetyl chloride with diazomethane and diazoethane, reflecting the increasing steric requirements, two aspects of which of which should be mentioned here. Reaction of trimethylacetyl chloride and diazomethane proceeded slowly but normally, under the proper conditions, to the diazo ketone (70% yield). With certain diazomethane solutions, however, trace impurities that had little or no effect with *n*- or isobutyryl chloride altered the course of reaction with trimethylacetyl chloride, giving chloromethyl *t*-butyl ketone (50–60% yield), even with an excess of diazomethane present.[7–9] Reaction of *diazoethane* with trimethylacetyl chloride gave several abnormal products instead of the diazo ketone, the latter being present at most only in small amounts.[5]

For rearrangement of these and other potentially sterically hindered diazo ketones, it was essential to

(1) For convenience in reference, we are now assigning to our earlier papers in the series Preparation and Reactions of Diazo Ketones the following numbers: (a) I, A. L. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948); (b) II, C. E. Blades and A. L. Wilds, *ibid.*, **21**, 1013 (1956); (c) III, A. L. Wilds, J. Van Den Berghe, C. H. Winestock, R. L. von Trebra, and N. F. Woolsey, *J. Amer. Chem. Soc.*, **84**, 1503 (1962); (d) IV, A. L. Wilds, N. F. Woolsey, J. Van Den Berghe, and C. H. Winestock, *Tetrahedron Lett.*, 4841 (1965).

(2) (a) Because of the higher reactivity of diazoethane (*vs.* diazomethane), it was found that lower temperatures (−20°) and limited amounts of diazohydrocarbon were necessary to avoid further reaction of the diazo ketone and diazoethane with loss of N_2 to form a mixed azine.[1a,2b,c,3] (b) A. L. Meader, Jr., Ph.D. Thesis, University of Wisconsin, 1947. (c) G. Baddeley, G. Holt, and J. Kenner, *Nature*, **163**, 766 (1949).

(3) P. Yates, D. G. Farnum, and D. W. Wiley, *Chem. Ind.* (London), 69 (1958).

(4) (a) W. E. Bachmann and J. C. Sheehan, unpublished work cited by W. E. Bachmann and W. S. Struve, *Org. Reactions*, **1**, 38 (1942). (b) This failure of mesitoyl chloride to react was confirmed by Van Den Berghe with diazomethane and diazoethane, 90–98% of the acid chloride being recovered. For details see ref 5.

(5) J. Van Den Berghe, Ph.D. Thesis, University of Wisconsin, 1952.

(6) R. C. Fuson, L. J. Armstrong, and W. J. Shenk, Jr., *J. Amer. Chem. Soc.*, **66**, 964 (1944).

(7) Distilled ethereal diazomethane prepared from N-methyl-N-nitrosourethan contained an impurity in trace amounts leading to the chloromethyl ketone. This impurity was removed by treatment with sodium ribbon and redistillation (see Experimental Section for procedure, also ref 5). The significance of these and related findings to the mechanism of diazo ketone and chloromethyl ketone formation has been discussed in theses.[5,8,9]

(8) C. E. Hummel, Ph.D. Thesis, University of Wisconsin, 1956; *Dissertation Abstr.*, **16**, 2305 (1956).

(9) N. F. Woolsey, Ph.D. Thesis, University of Wisconsin, 1961; *Dissertation Abstr.*, **22**, 3000 (1962).

use a reliable test method to get meaningful comparative results. Fortunately, the Wilds–Meader procedure[1a] for thermal Wolff rearrangement in homogeneous solution, heating the diazo ketone at 150–180° with a high-boiling alcohol and tertiary amine, provided such a test, giving reproducible results with a wide variety of diazo ketones; it avoided the occasional unreliability of the classical heterogeneous silver oxide and related catalyzed methods,[10] and the known structural limitations of the homogeneous silver salt–methanol–triethylamine procedure.[11] For examples closely related to the present series, normal rearrangement products were obtained from diphenylacetyldiazomethane and trimethylacetyldiazomethane.[5]

With triphenylacetyldiazomethane (**1**), however, the rearrangement took an abnormal course. After heating the diazo ketone with 1-hexanol and N-ethylmorpholine, two products were obtained, one the ester of the isomeric acid **2**, in which the acetic acid moiety is in the *ortho* position of one ring, and the other a related but dimeric ester, resulting from addition of one ring in the intermediate to that of the second monomer unit (Chart I).[1c,d] None of the normal product could be isolated from these *thermal* Wolff rearrangements under a variety of conditions.[12]

In this abnormal rearrangement, evidently the π-bond system of one aromatic ring, instead of the triphenylmethyl carbon, is providing the electrons for bonding to the diazo carbon (as N_2 is lost). *A priori*, this could be attributed either to an electronic effect (decreased electron availability on the triphenylmethyl carbon) or to a steric effect. The observations that diphenylacetyldiazomethane[5] and triphenylacetyl azide[8] underwent normal rearrangement in the thermal Wolff and Curtius processes, respectively, suggested (but did not establish) that the steric factor was important here.

As a further test of this steric factor, we looked at the synthesis and rearrangement of 9-phenylfluorene-9-carbonyldiazomethane (**5**), in which coplanarity of two rings reduces the steric impedance about the triaryl and carbonyl carbons without major change in the electronic environment. 9-Phenylfluorene-9-carboxylic acid (**4a**)[13] was prepared by metalation and carbonation of 9-phenylfluorene (**3a**).[14] The diazo ketone **5** resulted in good yield by reaction of the acid chloride with diazomethane.

When the diazo ketone **5** was heated with 1-hexanol and N-ethylmorpholine and the product hydrolyzed, two different acids of formula $C_{21}H_{16}O_2$ could be isolated, in approximately a 3:2 ratio. The former (mp 230°) was shown to be the normal rearrangement product, 9-phenylfluorene-9-acetic acid (**6a**), by comparison with an authentic sample prepared by fusion of 9-phenyl-9-fluorenol (**3b**) with malonic acid.[15,16] The two methyl esters also were identical.

The isomeric acid (mp 189°), by analogy to the triphenylacetyl series, could be the abnormal rearrangement product with the acetic acid function in the 1 position of the fluorene ring (**7a**), or the *ortho* position of the 9-phenyl group (**8**). Decarboxylation of the acid gave a hydrocarbon (mp 148–153°) which was shown to be 1-methyl-9-phenylfluorene (**9**) and not 9-*o*-tolylfluorene (**12**). Since both of these hydrocarbons were unknown,[17] authentic samples were prepared of each. By reaction of 1-methyl-9-fluorenone (**11**)[18] with phenyl Grignard reagent and reduction of the resulting carbinol (**10**) with zinc dust and acid, 1-methyl-9-phenylfluorene (**9**, mp 153–153.5°) was obtained. Reaction of *o*-tolyl Grignard reagent with 9-fluorenone, and reduction of the carbinol with zinc, gave authentic 9-*o*-tolylfluorene (**12**, mp 92.5–93.5°),[17] which was clearly different from the decarboxylation product. Infrared and nmr comparisons confirmed that the abnormal rearrangement product is the 1-acetic acid derivative **7**.

The nmr spectrum of the normal rearrangement product, as the methyl ester **6b**, showed, in addition to the expected 13 aryl hydrogens, singlets at δ 3.44 (CH_2) and 3.28 (OCH_3). The spectrum of the ester of the abnormal acid (**7b**) showed signals for only 12 aryl hydrogens, and a new singlet at δ 5.12 (triarylmethyl H), in addition to singlets at 3.53 (OCH_3) and 3.39 (CH_2).

The chemical shift for the methylene signal of the normal ester **6b** is upfield by 0.26 ppm compared with that for methyl β,β,β-triphenylpropionate (**13**, δ 3.70), reflecting the altered geometry of the three aryl rings in **6b**. Comparing the abnormal ester **7b** with the corresponding ester **2** (R = CH_3) in the triphenyl series, which showed a 14 aryl hydrogen multiplet, and singlets at δ 5.81 (triarylmethyl H) and 3.56 ($W_{h/2}$ 0.6 Hz, 5 H, CH_2 and OCH_3), the methylene signal of the former was shifted 0.17 ppm upfield, and the triarylmethyl hydrogen 0.69 ppm upfield. The triarylmethyl hydrogens showed typical line broadening ($W_{h/2}$ = 2.0 Hz), due to long-range coupling with the aryl hydrogens,[19] as did the methylene hydrogens of the fluorene derivative **7b** ($W_{h/2}$ = 1.4 Hz), but not of the triphenyl derivative **2**, as noted above.

It is not surprising that the chemical shifts of these triarylmethyl hydrogens vary widely. Because of their close proximity to three rings which can give either strong deshielding or shielding,[20] depending upon the geometry, their chemical shifts will be sensitive to structural changes affecting these rings. While this

(10) It is well known that even in the hands of experts an occasional silver oxide or related catalyzed Wolff rearrangement may fail to go, or give lowered yields, owing to unrecognized differences in the heterogeneous catalyst, and other factors.

(11) See M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.*, **72**, 5162 (1950).

(12) Wolff rearrangement by the photochemical method did give the normal rearrangement products both from diazo ketones **1** and **5**; for a preliminary discussion of this and related results, see ref 1c and 1d.

(13) H. Gilman, W. J. Meikle, and J. W. Morton, *J. Amer. Chem. Soc.*, **74**, 6282 (1952).

(14) F. Ullmann and R. von Wurstemberger, *Ber.*, **37**, 73 (1904).

(15) The comparable reaction of triphenylcarbinol with malonic acid was reported by L. Hellerman, *J. Amer. Chem. Soc.*, **49**, 1735 (1927).

(16) A study, after this part of our work was completed, of the reaction of triarylcarbinols including 9-phenyl-9-fluorenol with malonic acid has been reported by S. Patai and S. Dayagi, *J. Chem. Soc.*, 716 (1962), and following papers. For certain discrepancies with our results on the preparation of the acid **6a**, see Experimental Section.

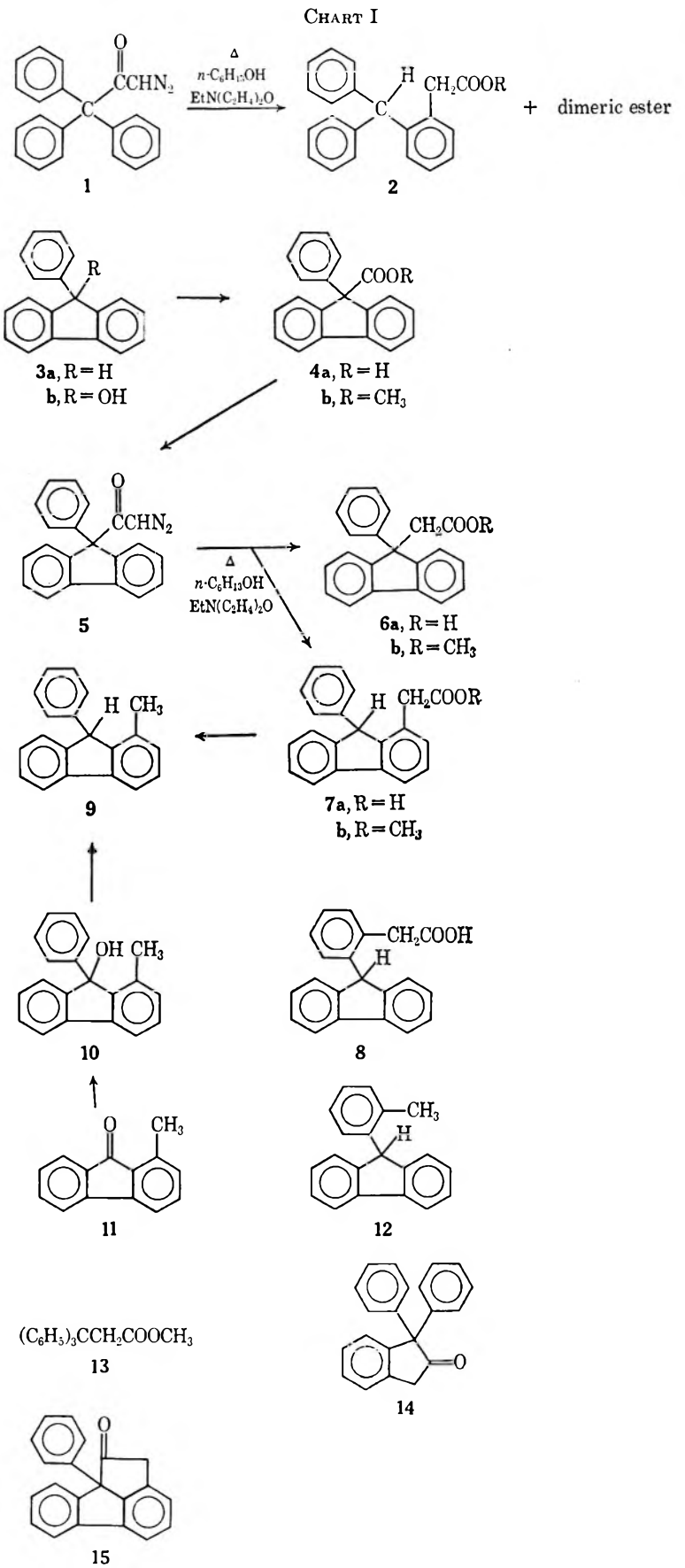
(17) The reported preparation of 9-*o*-tolylfluorene with mp 133° by R. Weiss and E. Knapp [*Monatsh. Chem.*, **61**, 61 (1932)] apparently is incorrect; further details on this compound and the temperature dependence of its nmr spectrum will be reported by N. F. Woolsey and S. Stepenske.

(18) W. C. Lothrop and P. A. Goodwin, *J. Amer. Chem. Soc.*, **65**, 363 (1943).

(19) See J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 592 (1963); E. Lustig and E. P. Ragelis, *J. Org. Chem.*, **32**, 1398 (1967), and references cited by them.

(20) See N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964; H. Suhr, "Anwendungen der kernmagnetischen Resonanz in der organischen Chemie," Springer-Verlag, Berlin, 1965, pp 33–36.

CHART I



signal for triphenylmethane comes at δ 5.44,[21] it is shifted to 5.03 for 9-phenylfluorene (**3a**), and 4.97 for 1-methyl-9-phenylfluorene (**9**). This signal for the ester **2** (R = CH_3) is shifted downfield 0.37 ppm from triphenylmethane, for the ester **7b** only 0.09 ppm downfield from 9-phenylfluorene.

The ester methoxy hydrogens for the triaryl substituted esters **6b** and **13** (δ 3.28 and 3.35) are clearly

(21) H. O. House and V. Kramar, *J. Org. Chem.*, **27**, 4146 (1962), and unpublished results of N. F. Woolsey.

shielded by the aryl rings, while those for esters **7b** and **2** (δ 3.53 and 3.56) come in the normal range for methyl esters.

The nmr spectrum of the decarboxylation product of **7a**, 1-methyl-9-phenylfluorene (**9**), showed in addition to the triarylmethyl hydrogen a singlet for the aryl methyl at δ 2.04, as did the authentic sample of **9** (δ 2.03, 3 H); the corresponding carbinol **10** had this aryl methyl signal at δ 2.08, each showing the usual aryl broadening. The nmr spectrum of 9-*o*-tolylfluorene (12) is quite different from those of the 1-methyl isomer **9** and the decarboxylation product of the acid **7a**.[17]

The thermal Wolff rearrangement of 9-phenylfluorene-9-carbonyldiazomethane (**5**) and isolation of products were carried out in several ways in an effort to find other abnormal products, or possible intermediates in the formation of the 1-acetic ester **7**. Chromatography of the products before hydrolysis led to small fractions with infrared spectra suggestive of a hydroxy ketone and a diketone, but no pure compounds could be isolated, except for a trace of 9-phenylfluorene. None of ketone **15** corresponding to direct cyclization of the diazocarbon at the 1 position could be found, and attempts to prepare this ketone by treatment of the diazo ketone **5** with boron trifluoride in ether were unsuccessful, although that procedure gave the indanone **14** in high yield from the diazo ketone **1**.[8]

Determination of the relative amounts of the normal and abnormal acids formed by rearrangement in the 9-phenylfluorene series was difficult, owing to problems of separation. Of the methods examined the best results were obtained by partition chromatography of the acids, the estimated yield of abnormal acid **7a** being about 35–40%, and of normal acid **6a** about 50–55%.

Isolation of 50–55% of the normal homologous product from Wolff rearrangement in the 9-phenylfluorene series **5** supports the contention that steric factors play an important part in preventing normal rearrangement of the more hindered diazo ketone **1** in the triphenylacetyl series. Normal rearrangement of other highly hindered diazo ketones mentioned previously, particularly trimethylacetyldiazomethane, occurs since no other lower energy path for reaction is available. The diazo ketones **1** and **5**, however, have sterically accessible π-electron clouds available in the aryl rings to compete with the electrons of the normally rearranging group.

Electronic as well as steric factors must play a part in favoring reaction at the more electron-rich 1 position of the fluorene ring to give **7**, instead of any significant amount of reaction in the 9-phenyl ring leading to **8**. Molecular models also indicate a preference for the diazo group to lie above the fluorene ring system and away from the phenyl ring. Additionally the greater entropy of activation for reaction in the more freely rotating phenyl ring should also contribute to the observed preference for **7**.

A few examples of other abnormal Wolff rearrangements have now been reported, involving silver-catalyzed procedures.[22] In two cases[22a,b] the products included acids isomeric with those expected, one being formed from a sterically hindered diazo ketone with a β,γ π-bond system (double bond) as for the thermal Wolff cases.

At the present time, the structural features which may result in abnormal Wolff rearrangement to an *acid derivative* seem to be twofold: (1) significant steric hindrance at the carbonyl or α carbon of the α′-diazo ketone, and (2) a π-bond system (aryl or double bond) at the β,γ position (suitably arranged for cyclization), which not only allows reaction in the γ position but also cleavage α to the carbonyl group. It may prove possible to enhance the reactivity at the γ position, relative to the α position, sufficiently to get abnormal products when steric hindrance is not so significant as with the present examples. Abnormal reaction (cyclization) may also be observed with certain hindered diazo ketones having the π-bond system at the γ,δ position, although in these cases acid derivatives would not be expected unless some other structural feature facilitated cleavage α to the carbonyl group.

For obtaining the normal rearrangement product, the thermal conditions of Wilds and Meader, as now modified,[1a,23] probably represent the procedure of greatest reliability and highest yield for most diazomethyl ketones, except for those with a high degree of steric hindrance, or leading to highly strained products, or sensitive to the higher temperatures. In these cases the photolytic conditions are preferable. For diazoethyl or higher diazo ketones, the thermal procedure seems to be superior to the photolytic method, which leads to appreciable amounts of unsaturated ketone.

Experimental Section

Melting points are corrected, determined with a Hershberg apparatus unless otherwise indicated; micro melting points were taken with a calibrated microscope hot stage. Uv spectra were run in 95% ethanol on a Cary Model 11 instrument and molecular extinction coefficients (ε) are reported. Ir spectra were run using a Baird Model B or a Perkin-Elmer Infracord (i) instrument. Nmr spectra were run at 60 MHz in deuteriochloroform with tetramethylsilane as internal standard using a Varian A-60A or A-60 instrument.

Preparation of Diazomethane.—For making diazo ketones from hindered acid chlorides,[5] diazomethane was prepared from N-methyl-N-nitrosourethan as described previously for diazoethane,[1a] by adding the nitrosourethan solution during 10 min while heating with an oil bath at 65°, then redistilled in the same apparatus while adding ether. The solution was dried with sodium ribbon at 0° for 1–2 hr, decanted and distilled once more as before. Diazomethane was determined by the benzoic acid method;[1a] over-all yields usually ranged from 60 to 75% when an electrically heated oil bath was used for heating during all distillations. Diazomethane for making methyl esters was prepared from N-methyl-N-nitrosourea without distillation.[24]

Determination of Diazo Nitrogen in Diazo Ketones.[25,26]—A solution of the diazo ketone (usually 30–50 mg) in 5 ml of tetraethylene glycol dimethyl ether (tetraglyme) was placed in the reaction flask of a special apparatus. The flask, magnetically

(22) (a) G. Eglinton, J. C. Nevenzel, M. S. Newman, and A. I. Scott, *Chem. Ind.* (London), 686 (1953); *J. Amer. Chem. Soc.*, **78**, 2331 (1956); see ref 1c, footnote 7; (b) A. Small, *J. Amer. Chem. Soc.*, **86**, 2091 (1964); (c) H. O. House, S. G. Boots, and V. K. Jones, *J. Org. Chem.*, **30**, 2519 (1965); (d) E. Wenkert, B. L. Mylari, and L. L. Davis, *J. Amer. Chem. Soc.*, **90**, 3870 (1968).

(23) Currently we prefer to use 1-hexanol or 1-octanol as the high-boiling alcohol and N-ethylmorpholine, γ-collidine or isoquinoline as the tertiary amine. It is not advisable to use benzyl alcohol as in the original procedure, since on standing traces of acid form and can interfere with the rearrangement reaction in sensitive cases. For compounds containing groups sensitive to alkaline hydrolysis of the resulting ester, we use triethanolamine as alcohol and amine,[1a] and hydrolyze the entire product with acid (see Experimental Section).

(24) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 165.

(25) This procedure was modified from earlier ones developed by Van Den Berghe[5] and Kraihanzel.[26]

(26) C. F. Kraihanzel, M.S. Thesis, University of Wisconsin, 1959.

stirred, was attached to a small, pressure equalizing dropping funnel with stopcock closure at the top and attached to a manometer and 10-ml gas buret, both filled with mercury (the total internal volume was about 75 ml of which 25 ml of the reaction flask was in a water bath). A freshly prepared mixture of 2.5 ml of 1:1 sulfuric acid–water solution and 2.5 ml of tetraglyme was placed in the dropping funnel, the mixture in the reaction flask was stirred and allowed to equilibrate in the water bath at room temperature for 30 min (room temperature controlled ±2°; bath ±0.1°), then the acid mixture was added to the reaction flask. Another 30 min was allowed for nitrogen evolution and reequilibration. The volume was corrected for any change in room or bath temperature; results were accurate to ±2% with 0.2-mmol samples.

9-Phenylfluorene-9-carboxylic Acid (4a).[13]—9-Phenyl-9-fluorenol (**3b**) was prepared from 9-fluorenone by the procedure of Ullmann and von Wurstemberger,[14] mp 110–111° (from 60–68° petroleum ether). Reduction with zinc dust and acetic and hydrochloric acids gave 94% 9-phenylfluorene **3a**:[14] mp 146.5–147.5°; nmr δ 7.67–7.83 (2 H, m, 4 and 5 aryl H), 6.95–7.55 (11 H, m, remaining aryl H), 5.03 (1 H, s, $W_{h/2}$ = 2.2 Hz, triarylmethyl H).

To 0.11 mol of *n*-butyllithium in ether was added a solution of 22.6 g (0.093 mol) of 9-phenylfluorene (mp 148–150°) in benzene, keeping the temperature below 10°. After stirring 1.5 hr at 25° the mixture was poured onto an excess of solid carbon dioxide and allowed to stand overnight. By isolation of the acidic fraction (95%) and recrystallization from benzene and petroleum ether (90–100°) 20.8 g (78%) of acid **4a** was obtained, mp 193.5–195°,[13] with additional material in the filtrates. Another crystalline form, mp 200–202.5°, also was obtained: mmp 194–196°; ir (i, $CHCl_3$) 5.85 (s, acid CO), 6.35, 6.69, 6.89 (w, m, ms, aryl rings), 7.14 (m), 8.93 (ms), 9.69 (w), 14.4 μ (s).

Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.92. Found: C, 84.14; H, 4.93.

The methyl ester **4b** was prepared with diazomethane and recrystallized from methanol: mp 164–165°; ir (i, $CHCl_3$) 5.75 (s, ester CO), 6.25, 6.69, 6.89, 6.97 (w, m, ms, ms, aryl rings), 8.18 (s), 8.54 (m), 9.80 (ms), 14.4 (ms); nmr δ 7.00–7.80 (13 H, m, aryl H), 3.74 μ (3 H, s, $W_{h/2}$ = 0.6 Hz, OCH_3).

Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.66; H, 5.25.

9-Phenylfluorene-9-carbonyldiazomethane (5).—A solution of 5.0 g of 9-phenylfluorene-9-carboxylic acid (**4a**) in 11.5 ml of pure thionyl chloride was refluxed for 9 hr, then concentrated under reduced pressure at 25°, followed by addition and similar evaporation of two to four 25-ml portions of dry benzene to ensure complete removal of thionyl chloride (odor); the crude acid chloride was used, 5.2 g (95%), mp 87–90°, Cl 11.70% (calcd 11.63%).

A solution of 5.2 g (17 mmol) of acid chloride in 50 ml of ether and 50 ml of benzene (both anhydrous) was added over 30 min at 0° to a stirred solution of 96 mmol of sodium-dried diazomethane in 315 ml of ether. While stirring for 30 min more at 0° the yellow diazo ketone precipitated. After removal of excess diazomethane and some of the solvent under reduced pressure at 0°, 4.1 g of pale yellow diazo ketone **5** was obtained, mp 153.5–154.5° (diazo N_2 97%). A second crop of 0.75 g from benzene–petroleum ether made a total of 92%. Recrystallization of the first crop from benzene–petroleum ether raised the melting point to 159–160° (diazo N_2 99%).

Rearrangement of 9-Phenylfluorene-9-carbonyldiazomethane (5).—A mixture of 1.10 g of the diazo ketone **5** (mp 155.5–156.5°), 5 ml of 1-hexanol and 5 ml of N-ethylmorpholine (each solvent redistilled) was placed in the reaction flask, attached through a reflux condenser to a large gas buret. The flask was then immersed in an oil bath preheated to 175–180°, and heated at that temperature for 15–25 min (N_2 evolution 93% of theory, over in 6 min). After dissolving in ether and washing with dilute acid (1:2 HCl), the solvent and 1-hexanol were removed, finally by azeotropic distillation with xylene and benzene. The residue in benzene–petroleum ether (1:5) was chromatographed on 100 g of alumina (Woelm), collecting 30-ml fractions. After a small amount (14 mg) of 9-phenylfluorene in fractions 13–15, eluted with 1:1 benzene–petroleum ether, the next major fractions (35–42, eluted with 15:1 benzene–petroleum ether) contained a green oil (0.63 g) having an ir spectrum closely resembling that of *n*-hexyl 9-phenylfluorene-9-acetate (see below). Hydrolysis with 7 g of potassium hydroxide in 13 ml of 50% methanol at reflux for 5 hr gave, after dilution, ether extraction and acidification, 0.44 g of pale green solid, mp 200–220°, a mixture containing mainly the normal acid **6a**.[27] Fractions 43–73 (0.11 g, eluted with ether and then chloroform) of hydrolysis gave 0.09 g of an acid mixture. Fraction 76, eluted with 10:1 chloroform–acetone, gave 15 mg of an oil, ir ($CHCl_3$) 5.80 (s, CO), 6.00 (ms, conjugated CO), 6.23, 6.69, 6.88 μ (w, m, s, aryl rings), which suggested a diketone, although no solid quinoxaline derivative could be obtained. Fractions 77–78 (44 mg) and 79 (28 mg) [ir ($CHCl_3$) 2.75, 2.90 (w, w, OH), 5.85 (ms, CO), 6.10 (ms, conjugated CO), 6.25 (shoulder), 6.70, 6.89 μ] were suggestive of a ketol. Further elution with chloroform–acetone mixtures and acetone alone gave in fractions 80–91 a total of 108 mg (after evaporation of acetone condensation products), of which 4 mg was solid, micro mp 134–141°. Fraction 91 (32 mg), which appeared from the ir spectrum to contain a ketol, was acetylated with acetic anhydride (ir 5.72, acetate CO) but still could not be crystallized.

Since a previous run had shown that part of the product was converted into the salt and held on the adsorbent, the alumina was digested with 5% potassium hydroxide for 30 min on the steam bath, filtered, acidified with dilute hydrochloric acid until all the aluminum hydroxide was in solution, then extracted with ethyl acetate. The resulting product was recrystallized twice from ethyl acetate–petroleum ether and from chloroform–petroleum ether to give 0.13 g of solid, mainly the abnormal acid **7a**, micro mp 175–177°. Treatment with diazomethane and recrystallization from dilute methanol gave the abnormal methyl ester **7b**, mp 97–100° (mixture melting point not depressed).

In another run, the neutral fraction of the rearrangement product was hydrolyzed with 20 ml of 20% potassium hydroxide in 50% methanol at reflux for 4 hr, the acidic fraction isolated (66%) and the neutral fraction rehydrolyzed twice, giving further acidic fractions (25 and 9%). Aliquots of these fractions were carried through partition chromatography on silicic acid (using 9:1 $HCONH_2$–0.5 *N* H_2SO_4 as the stationary phase and 10% CCl_4 in petroleum ether as the mobile phase).[28] From the first hydrolysis product was obtained 13% of oily acid (fractions 1–26), 39% of crystalline acid (fractions 27–38), micro melting points ranging from 173 to 178°, mainly the abnormal acid **7a**, then 3% of oil (fractions 39–40) and 26% of solid (fractions 41–53), micro melting points ranging from 194 to 210°, mainly the normal acid **6a**. Recrystallization of appropriate fractions from dilute methanol gave 28% of the abnormal acid **7a**, mp 184–189°, and 21% of normal acid **6a**, mp 225–228°.

By similar separation, the combined second and third hydrolysis fractions gave mainly the normal acid **6a**, an additional 20–25% being obtained before recrystallization, with micro melting points ranging 185–227°.

In summary, the best estimates for the acids present after hydrolysis of the thermal rearrangement product using 1-hexanol and N-ethylmorpholine are 50–55% of the normal acid **6a**, and 35–40% of the abnormal acid **7a**, of which about two-thirds of each could be obtained in reasonably pure form by recrystallization of the acids or methyl esters. Other methods of separation or estimation of the isomers were less satisfactory.[29]

In other rearrangment runs the diazo ketone **5** was heated with triethanolamine[15] at 180–185° from 15–20 min; then the entire product was hydrolyzed by heating with dilute hydrochloric acid (1:1) at reflux for 5 hr, giving 75–80% of the crude acid mixture, mp 170–195°, from which the same abnormal acid **7a**, mp 187–190°, methyl ester **7b**, mp 100.5–101°, and the normal acid ester **6b**, mp 91–92°, could be isolated by chromatography of the methyl esters on alumina as described above, including alkaline digestion of the adsorbent to obtain the abnormal acid.

Methyl 9-Phenylfluorene-1-acetate (7b) from Rearrangement of 5.—By recrystallization of the abnormal methyl ester (**7b**) the purest sample was obtained as small, colorless needles or

(27) Further hydrolysis of the neutral fraction gave more of the acid (*cf.* below).

(28) This procedure is a modification of that of P. M. Bhargava and C. Heidelberger, *J. Amer. Chem. Soc.*, **77**, 166 (1955); see also H. G. Cassidy in "Technique of Organic Chemistry," Vol. 5, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1951, p 291.

(29) At the time this part of the work was completed (1960) good integrated nmr spectra were not possible with our instrumentation, nor was satisfactory resolution of the methyl esters by glpc possible with equipment then available. If future work is done, either of these methods should be satisfactory with the techniques now available. Since the product composition probably varies some with conditions of rearrangement, it does not seem necessary to obtain higher accuracy for present purposes.

rods from dilute methanol: mp 100.6–101.4° (vacuum dried at 80°); mixture melting point with methyl 9-phenylfluorene-9-acetate was depressed to 70–80°; there was evidence of a second crystalline form melting around 84–85°; uv max 269 mμ (ε 17,100), 281.5 (10,000), 292.5 (5170), 304 (7200); shoulders 236, 259, 265, 275; uv min 242, 280, 288, 299; ir ($CHCl_3$) 5.78 (s, ester, CO), 6.23, 6.65, 6.85, 6.94 μ (m, m, ms, ms, aryl rings); ir (CS_2) 5.73 (s), 13.22–13.31 (s), 13.58 (m), 14.34 μ (s); nmr δ 7.65–7.85 (2 H, *m*, 4 and 5 aryl H), 6.90–7.55 (10 H, m, remaining aryl H), 5.12 (1 H, s, $W_{h/2}$ = 2.0 Hz, triarylmethyl H), 3.53 (3 H, s, OCH_3), 3.39 (2 H, s, $W_{h/2}$ = 1.4 Hz, CH_2).

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.96; H, 5.86.

The purest sample of the **abnormal acid 7a**, from partition chromatography and recrystallization from dilute methanol, was obtained as colorless needles, mp 188.5–189.5°.[30]

9-Phenylfluorene-9-acetic Acid (6a). A. From Rearrangement of 5.—Recrystallization of a sample of the normal acid from benzene–petroleum ether (bp 90–100°) and from dilute methanol gave colorless material: mp 227.5–230°; mixture melting point with an authentic sample (see below) was undepressed; uv max 236 (ε 12,800), 267 (14,400), 270 (14,600), 294 (4800), 305 (7100), 278 mμ (sh); uv min 234, 244, 289, 300 mμ.

The **methyl ester (6b)** of the normal acid, prepared with diazomethane and recrystallized from dilute methanol, melted at 91.5–93°; mixture melting point with an authentic sample (see below) was undepressed.

B. From 9-Phenyl-9-fluorenol (3b).—Several runs were made under varying conditions using malonic acid and 9-phenyl-9-fluorenol (**3b**, mp 109.5–110.5°) in equal weights, or three times as much malonic acid, and heating at 160–170° for periods of 0.5–3.5 hr. Although the crude acid was obtained in as high as 97% yield, mp 205–225°, it was not pure; separation from the accompanying impurity was difficult.[16] Recrystallization from benzene–acetic acid gave 50% of solid, mp 227.5–229.5°, which was mainly the desired acid **6a**, while the material in the second and third crops melted below 210°.[31] Purification of the acid was difficult, the best material being obtained by recrystallization both as the methyl ester and the acid, the latter from ethanol, mp 229–230°.

The **methyl ester 6b** was recrystallized from petroleum ether: mp 91.5–92.5°; ir ($CHCl_3$) 5.79 (s), 6.95 μ (s); ir (CS_2) 5.76, 8.38, 8.62–8.72, 13.24, 13.43, 13.60, 14.40; nmr δ 7.65–7.85 (2 H, m, 4 and 5 aryl H), 7.10–7.55 (11 H, m, remaining aryl H), 3.44 (2 H, s, $W_{h/2}$ = 0.8 Hz, CH_2), 3.28 (3 H, s, OCH_3).

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.02; H, 5.74.

The ***n*-hexyl ester** was prepared by refluxing a solution of the acid in *n*-hexanol containing some sulfuric acid. The crude product, after washing and drying, was evaporatively distilled in a sublimation apparatus at 180° (0.1 mm): ir (in oil) max 5.81 (s, CO), 6.70, 6.91, 7.85, 8.66, 8.77, 14.43 μ (all m).

Decarboxylation of the Abnormal Acid 7a to 1-Methyl-9-phenylfluorene (9).—A mixture of 82 mg of 9-phenylfluorene-1-acetic acid (**7a**, mp 187–189°), 0.5 g of copper powder and 5 ml of redistilled isoquinoline was heated at 225° for 1 hr and at 235° for 15 min, then cooled, diluted with benzene, filtered and washed with acid and base. The neutral fraction was sublimed twice at 0.02 mm; then the oily solid (19 mg) was chromatographed on 3 g of alumina (Woelm), using petroleum ether. In fractions 2–9 was obtained 13 mg of solid which was recrystallized from dilute ethanol to give 6 mg, micro mp 148–153°. A mixture with authentic 1-methyl-9-phenylfluorene (see below) melted at 150–153°. The infrared spectra of the two samples in KBr were essentially identical. The nmr of a less pure sample, mp 148–152°, showed the methyl signal at δ 2.04 (smaller peaks at δ 1.27 and 1.50 due to a persistent impurity).

1-Methyl-9-fluorenone (11).—2-Acetylamino-2′-methylbenzophenone was prepared in 52% yield by the procedure of Lothrop and Goodwin,[18] and hydrolyzed. The total crude amine from 8.63 g of the acetylamino compound was treated in 700 ml of 50% sulfuric acid at −5° with 2.5 g of sodium nitrite; then after 1 hr at −5°, the solution was heated to 60–70° on the steam bath for 2 hr. Isolation of the product by chromatography as reported[18] and recrystallization from petroleum ether gave 4.30 g, mp 98–100° (lit.[18] mp 98°), and 0.50 g, mp 97–100°, for a total of 73%.

1-Methyl-9-phenyl-9-fluorenol (10).—Following the procedure for 9-phenyl-9-fluorenol,[14] to an excess of phenyl Grignard reagent in ether was added 1-methyl-9-fluorenone in benzene–ether solution. The resulting carbinol (79%, mp 134–136°) was recrystallized from petroleum ether: mp 136.5–137°; ir ($CHCl_3$) max 2.74 (OH), 6.71, 6.90, 8,60, 9.77, 14.34 μ; nmr δ 6.90–7.70 (12 H, m, aryl H), 2.19 (1 H, broad s, OH), 2.08 (3 H, s, $W_{h/2}$ = 1.4 Hz, CH_3).

Anal. Calcd for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.32; H, 5.83.

1-Methyl-9-phenylfluorene (9).—A solution of 1.20 g of the fluorenol **10** in 16.5 ml of acetic acid and 20 ml of 25% hydrochloric acid was heated at reflux with 1.15 g of zinc dust for 3 hr, then decanted and the zinc washed with hot acetic acid. Cooling the solution gave 0.78 g, mp 152–153.5°, and an additional 0.08 g (total 91%) on dilution and recrystallization. Three recrystallizations from ethanol gave the analytical sample: mp 153–153.5°; ir (KBr) 6.95, 12.51, 13.12–13.35, 13.6 μ; nmr δ 7.55–7.85 (2 H, m, 4 and 5 aryl H), 6.90–7.50 (10 H, m, remaining aryl H), 4.97 (1 H, s, $W_{h/2}$ = 1.7 Hz, triarylmethyl H), 2.03 (3 H, s, $W_{h/2}$ = 1.6 Hz, CH_3).

Anal. Calcd for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.79; H, 6.38.

Registry No.—**4a**, 18554-43-3; **4b**, 18554-44-4; **5**, 18554-45-5; **6a**, 18554-46-6; **6b**, 18554-47-7; ***n*-hexylester of 6a**, 18554-48-8; **7a**, 18554-18-2; **7b**, 18554-49-9; **9**, 18554-50-2; **10**, 18554-51-3.

Acknowledgments.—We are indebted to Mrs. Armida Giumanini for running the nmr spectra. We also wish to express our thanks for financial support of parts of this work by the National Science Foundation, the U.S. Public Health Service, and the Wisconsin Alumni Research Foundation through the University of Wisconsin Research Committee.

(30) There were indications of a second crystalline form melting around 230–240°, and possibly a third at 175–176.5°.

(31) The nmr spectra of these fractions of the acid showed two CH_2 singlet peaks, at δ 3.37, corresponding to the normal acid, and at 3.31, in ratios of 55–60 to 45–40%. The second peak may be due to acid **7a** in this reaction also, as a result of reaction of the intermediate carbonium ion in the 1 position, or the isomeric 3-acetic acid derivative.

New Photochromic Cyclohexadienes

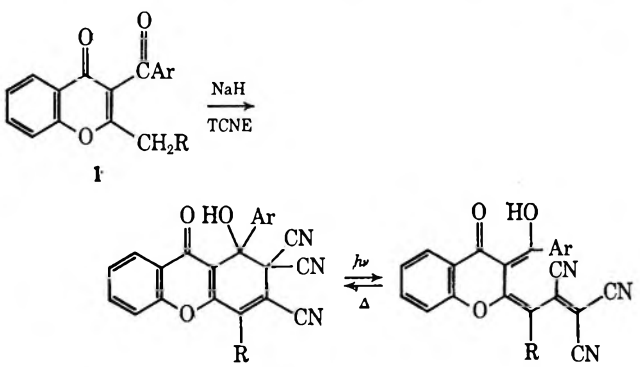
K. R. HUFFMAN,[1] M. BURGER, W. A. HENDERSON, JR., M. LOY, E. F. ULLMAN

Chemical Department, Central Research Division, American Cyanamid Company, Stamford, Connecticut 06904

Received September 9, 1968

The effect of structural modification on the behavior of highly substituted cyclohexadienes has been studied. The new photochromic compounds, prepared by condensation of *vic*-alkylaroyl heterocycles with tetracyanoethylene and related olefins, include 2,2-dicyano-1,2-dihydro-9-xanthenones, 2-cyano-1,2-dihydro-9-xanthenone-2,3-dicarboximides, 1,2- and 3,4-dihydrotricyanodibenzofurans, and a 1,2-dihydro-2,2,3-tricyano-9-acridone. In addition the synthesis of some new 4-alkyl-3-benzoylcoumarins and 4-alkyl-3-benzoylcarbostyrils has provided further examples of photochromic *vic*-alkylaroyl heterocycles. The color forming efficiencies and thermal fading rates of several of the photochromic cyclohexadienes are reported and their photochemical behavior at −196° in rigid media is described.

The synthesis of several highly substituted 1,2-dihydro-9-xanthenones (**2**) has recently been described[2] and the dramatic photochromic behavior of these compounds has been characterized as a reversible cyclohexadiene–hexatriene valence isomerization process (**2** ⇄ **3**).



a, R = Ar = Ph

The most convenient preparation of compounds of structure **2** was found to be the base-promoted condensation of 3-aroyl-2-alkylchromones (**1**) with tetracyanoethylene. This reaction presumably proceeds *via* an addition–elimination mechanism[3] involving addition of the anion of the chromone to the olefin, followed by loss of cyanide and subsequent ionization to give the anion of the product. Upon acidification, the cyclic photochromic material (**2**) is obtained.

In principle, it appeared that electronegatively substituted olefins other than tetracyanoethylene should undergo similar reactions with **1**, provided that a reasonably good leaving group was present. Moreover, one could envision a series of analogous compounds derived from various *vic*-alkylaroyl heterocycles other than chromones. If the cyclohexadiene moiety of **2** were the only feature necessary for the photosensitivity of the system, modifications such as these could provide a series of photochromic compounds encompassing a wide range of properties. The present investigation was designed to determine the scope of the reaction and to study the effect of structural modifications on factors such as position and intensity of the visible maxima of the colored forms, efficiency of the photochemical ring opening, return rates, and photochemical stability.

(1) To whom all correspondence should be addressed.

(2) (a) K. R. Huffman, M. Loy, W. A. Henderson, Jr., and E. F. Ullman, *Tetrahedron Lett.*, 931 (1967); (b) K. R. Huffman, M. Loy, W. A. Henderson, Jr., and E. F. Ullman, *J. Org. Chem.*, **33**, 3469 (1968).

(3) See S. Patai and Z. Rappoport in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1964, pp 526 ff.

1,2-Dihydro-9-xanthenones.—The reaction of the 3-aroyl-2-alkylchromones **1a–e** with methoxymethylene malononitrile or ethoxymethylenemalononitrile was found to proceed in the manner analogous to that previously seen with tetracyanoethylene.[2] The resulting 2,2-dicyano-1,2-dihydro-9-xanthenones, **4** (Table I), were characterized by ultraviolet (Table II) and infrared spectra. These compounds were all photochromic at room temperature in nonbasic solvents, but their behavior differed significantly from the corresponding 2,2,3-tricyano analogs.[2]

The effect of the presence or absence of the 3-cyano group can best be illustrated by comparison of the two diphenyl derivatives **2a** and **4a**. Brief ultraviolet irradiation of dilute benzene solutions of **2a** led to intensely red solutions (λ^*_{max} 532 mμ), which faded to colorless within a few seconds in the dark.[2] When freshly prepared solutions of **4a** were treated in the same manner, an intense yellow-orange color (λ^*_{max} 420 mμ) was produced, which by analogy must be the ring-opened tautomer **5a** (or a geometrical isomer). The latter solutions faded in the dark over a period of several hours, but did not return completely to the original colorless state. On brief heating and subsequent cooling of solutions of **4a** similar color changes were observed, and the color intensities ultimately attained were equal to those resulting from fading of the same solutions after photochemical activation.

These results indicate that the colored form **5a** is present in equilibrium with **4a**. However, unlike the tricyano compounds, which are nearly colorless in nonpolar solvents at room temperature, the **4a** ⇄ **5a** equilibrium is displaced sufficiently toward **5a** to impart considerable color to the solutions (Chart I). This difference in the two groups of compounds is probably steric in nature. Thus in the colored forms of the dicyano compounds (**5**), it is clear that there is much less hindrance to planarity of the hexatriene system than in the tricyano compounds. This is manifest in the higher intensity visible absorption maxima of the dicyano compounds in alcoholic solution (**5a**, ε 39,000; **3a**, ε 12,000),[2b] where they apparently exist largely in the ionized form of the trienes (see ref 2b and Table II).

In other respects the behavior of the dicyano compounds **4** was similar to that previously observed for **2**. Reaction of **4a** and **4d** with acetic anhydride gave the acetates **6a** and **6d** (Table III). Solutions of these acetates did not become colored on heating or standing, but, like the tricyanoacetate **8**, they became intensely colored upon irradiation and the colored solutions faded at a minimal rate at room temperature in the dark.

TABLE I

PRODUCTS FROM THE CONDENSATION OF *vic*-ALKYLAROYL HETEROCYCLES WITH ELECTRONEGATIVELY SUBSTITUTED OLEFINS

Compd	Reaction time, hr	Yield, %	Mp, dec, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4a	4[a]	49	175.5–177	$C_{27}H_{16}N_2O_3$	77.87	3.87	6.73	77.61	3.69	6.83
4b	6[b]	46	166.5–169.5	$C_{28}H_{18}N_2O_4$	75.32	4.06	6.28	75.15	4.13	6.06
4c	6[b]	30	159–162	$C_{28}H_{18}N_2O_4 \cdot H_2O$	72.40	4.34	6.03	72.35	4.24	6.05
4d	5.5[b]	35	190.5–193.5	$C_{22}H_{14}N_2O_3$	74.56	3.98	7.91	74.52	3.89	7.95
4e	6[b]	19	190.5–192.5	$C_{23}H_{16}N_2O_4$	71.87	4.20	7.29	71.52	4.35	7.38
12	2.5[a]	47	232–234	$C_{28}H_{16}N_2O_5 \cdot H_2O$	70.29	3.79	5.86	70.17	3.48	5.81
18	1.5[a]	20	>210	$C_{29}H_{18}N_4O_2 \cdot CH_2Cl_2$	66.80	3.73	10.39	66.23	3.91	10.44
21	1[a]	57	187.5–188.5	$C_{27}H_{15}N_3O_2$	78.44	3.66	10.16	78.41	3.69	10.21
36	3[a]	33	>180	$C_{29}H_{18}N_4O_2$	76.64	3.99	12.33	76.81	4.22	12.23

[a] In tetrahydrofuran. [b] In benzene.

TABLE II

SPECTRAL DATA FOR CYCLOHEXADIENE COMPOUNDS

Compd	$\lambda_{max}^{CH_2Cl_2}$, mμ (log ε)[a]	$\lambda_{max}^{CH_3OH}$, mμ (log ε)[b]	$\lambda^{*C_6H_6}_{max}$, mμ
4a	260 (4.27), 308 (3.98)[d]	309 (4.10), 453 (4.59)	420
4b	264 (4.40), 309 (4.09), 323 sh, (4.06)[d]	312 (4.16), 465 (4.60)	431
4c	260 (4.32), 307 (4.00)[d]	301 (4.24), 464 (4.54)	435
4d	259 (4.17), 265 (4.20), 306 (3.98)[d]	309 (3.99), 461 (4.47)	408
4e	256 (4.22), 264 (4.22), 300 (4.09)[d]	296 (4.20), 461 (4.41)	417
6a	257 (4.29), 304 (4.00)	*e*	452, 474, 506
6d	256 (4.27), 262 (4.28), 296 (4.00), 320 sh (3.81)	*e*	457
12	273 (4.17), 321 (4.06)	308 (4.05), 492 (3.88)	549
15	275 (4.08), 323 (4.03)	*e*	550
16	269 (4.22), 320 (4.11)	304 sh (4.06), 492 (3.97)	550
18	250 sh (4.27), 276 (4.30), 288 (4.32), 336 (4.08), 420 (3.63)	245 (4.60), 345 (4.24), 424 (3.96)	*f*
21	244 (4.20), 367 (4.30)	255 sh (4.30), 298 (4.11), 316 sh (4.06), 372 (4.00), 482 (4.06)	*f*
22	234 sh (4.17), 254 sh (4.04), 324 sh (4.06), 366 (4.27), 380 sh (4.19)[g]	*e*	553
25	251 (4.40), 295 (3.88), 344 (3.74)	329 (4.26), 369 sh (4.10), 485 (3.62)	*f*
26	255 (4.56), 296 (4.06), 340 sh (3.87)	*e*	637
36	237 (4.53), 263 (4.25), 296 (3.84), 345 (3.93), 410 sh (3.59)	230 sh (4.64), 282 sh (4.08), 359 (4.24), 445 sh (3.65)	*f*

[a] In Baker & Adamson reagent grade methylene chloride. [b] In methanol containing 0.1% water. [c] Visible maxima of the colored forms obtained by ultraviolet irradiation at 15–25°. Values are approximate only, as most of the bands were broad and somewhat flat. [d] The spectra of **4a–e** in methylene chloride were run on freshly prepared solutions so as to minimize thermal conversion into the colored modification. [e] No solvatochromism. [f] Not photochromic at room temperature. [g] In cyclohexane.

TABLE III

ACETOXYDIHYDROXANTHENONES AND -DIHYDRODIBENZOFURANS

Compd	Yield, %	Mp, dec, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6a	68	184–185[a]	$C_{29}H_{18}N_2O_4$	75.97	3.96	6.11	75.83	4.04	6.27
6d	70	191.5–192[a]	$C_{24}H_{16}N_2O_4$	72.72	4.07	7.07	72.77	4.17	7.02
15	90	221–222[b]	$C_{30}H_{18}N_2O_6 \cdot 0.5H_2O$	70.45	3.74	5.48	70.79	3.74	5.61
22	97	225.5–226.5[b]	$C_{29}H_{17}N_3O_3$	76.47	3.76	9.23	76.36	3.84	9.02
26	90	230–231[b]	$C_{29}H_{17}N_3O_3$	76.47	3.76	9.23	76.19	3.73	8.94

[a] Recrystallized from ethanol. [b] Recrystallized from methylene chloride–petroleum ether (bp 30–60°).

Upon preparative scale photolysis of **6d**, an isomeric compound was obtained as a stable, intensely purple crystalline solid. The structure **7d** was assigned to this product by analogy with the photochemical conversion of **8** into **9**.[2] The infrared spectrum of **7d** showed the expected maxima at 4.54, 5.67, and 6.00 μ, corresponding respectively to nitrile, enol ester, and chromone carbonyl absorptions.

Photochemical bleaching of **5** or **7** appeared to be negligible as previously found in the tricyano series. However, the smooth photochemical conversion of the tricyano compound **2a** into a bicyclo[3.1.0]hexene derivative (**10**)[2b,4] apparently was not duplicated in the dicyano series. Thus, a 100-mg sample of **4a** in benzene required 40-hr irradiation with ultraviolet light from a high-pressure mercury arc before the photochromic activity was completely destroyed and no pure photodecomposition products could be isolated from the resulting mixture. By contrast, photolysis of **2a** under the same conditions resulted in a >80% isolated yield of photoisomer **10** after 2 hr, with complete loss of photochromic activity of the solution. This difference in

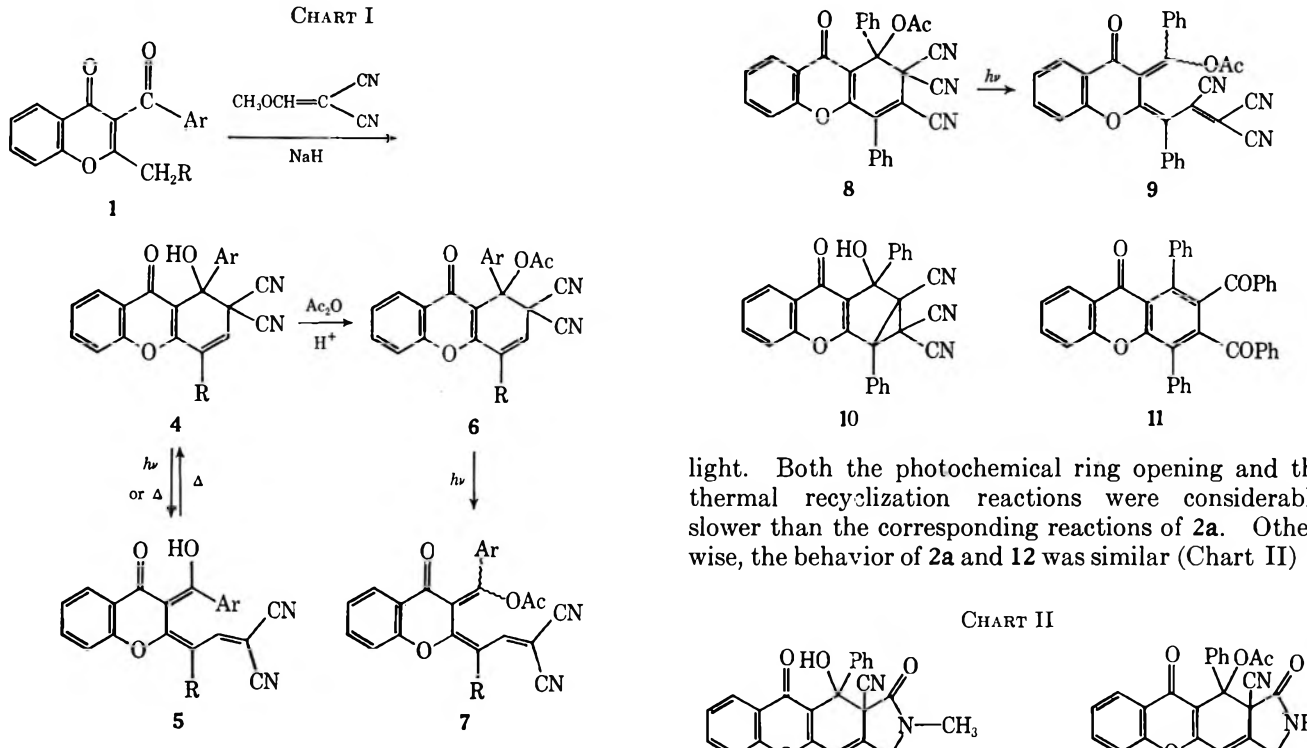
(4) E. F. Ullman, W. A. Henderson, Jr., and K. R. Huffman, *Tetrahedron Lett.*, 935 (1967).

TABLE IV
PHOTOCHEMICAL DATA

Compd	Photochromism[a] −196°	Photochromism[a] +20°	k^{-1}, sec^{-1}[b]	$\Phi\epsilon$[c]
2a	Blue	Red	8.8×10^{-2}	25,000[f]
				26,000[g]
4a	Red-orange	Orange	1.7×10^{-3}	12,000[f]
				11,000[g]
4b	Red	Orange	1.4×10^{-3}	15,000[g]
4d	Yellow	Yellow	4.2×10^{-4}	11,000[g]
6a	*d*	Red-orange	$<1 \times 10^{-7}$	8,900[f]
6d	*d*	Red-orange	$<1 \times 10^{-7}$	9,300[f] (ϕ = 0.54)
8	*d*	Purple	6.2×10^{-6}	620[f] (ϕ = 0.029)
22	Blue-green	Purple	*e*	*e*
26	Green	Blue	2.7×10^{-1}	16,000[g]

[a] Color observed upon irradiation of compounds in a solvent of approximately equal volumes of toluene–methylcyclohexane–isopentane. [b] First-order rate of thermal bleaching reaction in benzene at 25° measured as described in ref 2b. [c] Quantum yield of color formation times extinction coefficient of visible maximum in benzene. See ref 2 b for description of methods. [d] Photochromic in liquid solutions only. [e] Fading rate too fast to measure. [f] Method I.[2b] [g] Method II.[2b]

CHART I



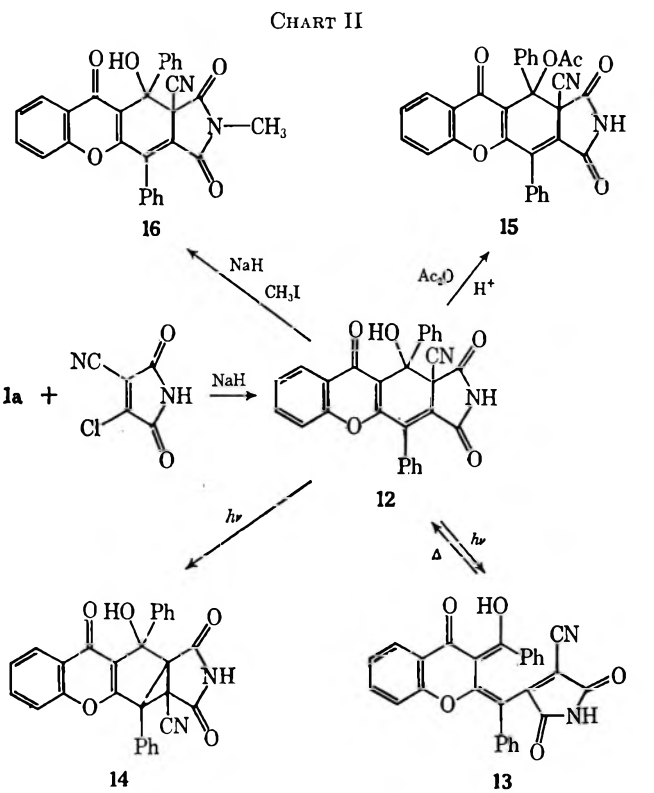
1

a, R = Ph; Ar = Ph
b, R = *p*-CH_3OPh; Ar = Ph
c, R = Ph; Ar = *p*-CH_3OPh
d, R = CH_3; Ar = Ph
e, R = CH_3; Ar = *p*-CH_3OPh

reactivity is not surprising, as it had been previously demonstrated[2a,4] that the formation of **10** proceeds directly from light absorption by **2a**. Since the efficient photochemical process **4a** → **5a** (see Table IV) coupled with the relatively slow thermal process **5a** → **4a** results in a low photostationary concentration of **4a**, other efficient photochemical reactions of this isomer would be unlikely.

Condensation of 3-benzoyl-2-benzylchromone (**1a**) with 2-chloro-3-cyanomaleimide resulted in formation of the dihydroxanthenone **12**, which also exhibited photochromism at room temperature, giving deep purple solutions ($\lambda^{*C_6H_6}_{max}$ 549 mμ). The purple color (**13**) faded within a few hours in the dark and was not noticeably destroyed by irradiation with visible light. Both the photochemical ring opening and the thermal recyclization reactions were considerably slower than the corresponding reactions of **2a**. Otherwise, the behavior of **2a** and **12** was similar (Chart II)

CHART II



16 15 1a + 12 14 13

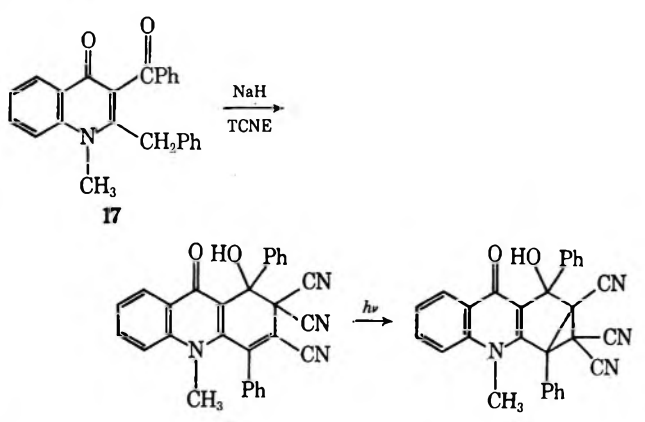
Prolonged irradiation of **12** converted it irreversibly into a photoisomer which was assigned structure **14** on the basis of spectral data (Experimental Section) and analogy with the photoisomerization of **2a**.

Acetylation of **12** afforded the O-acetate **15** which became permanently colored ($\lambda^{*C_6H_6}_{max}$ 550 mμ) upon irradiation. Compound **12** was also transformed into the N-methyl derivative **16**, by conversion into the dianion with sodium hydride, followed by treatment with methyl iodide. Like **12**, the N-methyl analog **16** was photochromic, but generation of the colored form appeared to be much less efficient.

Several other electronegatively substituted olefins, analogous to tetracyanoethylene or methoxymethylenemalononitrile, were prepared by literature methods and subjected to reaction with **1a** according to the usual procedure. Compounds such as 4-(tricyanovinyl)-N,N-dimethylaniline,[5] diethyl ethoxymethylenemalonate, and 1,1-dicyano-2,2-dimethoxyethylene[6] failed to condense with **1a** under these conditions. The reaction of **1a** with 2,3-dicyano-1,4-naphthoquinone[7] produced a small amount of uncharacterized, nonphotochromic material.

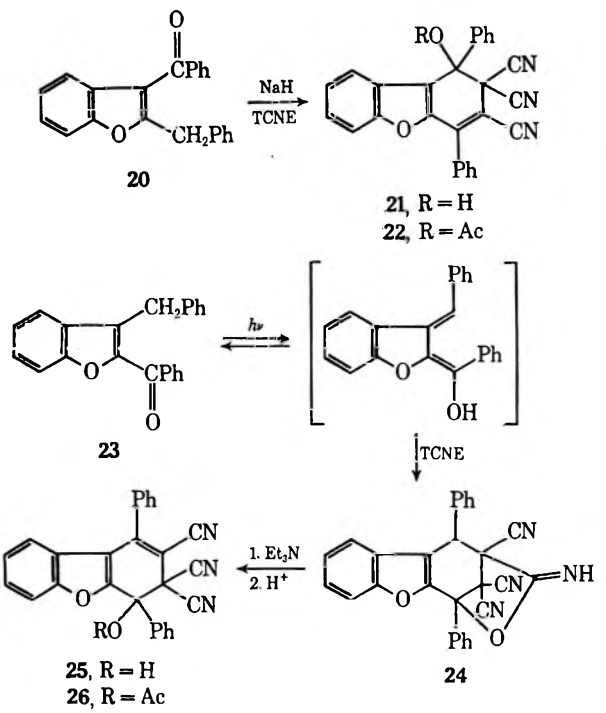
On the other hand, the condensation of **1a** with chlorotribenzoylethylene,[8] a compound with a better leaving group than most of the above examples, proceeded smoothly to give a good yield of crystalline product. However, this material proved to be the nonphotochromic aromatized xanthenone **11**, derived from formal loss of the elements of benzoic acid from the desired product.

1,2-Dihydro-9-acridones.—As an example of an analog containing a nitrogen atom in place of the heterooxygen of **2**, the 1,2-dihydro-9-acidone compound **18** was prepared from the quinolone **17**[9] and tetracyanoethylene. The yellow **18** was not photochromic at room temperature, but, at temperatures below −50° in methylene chloride, it became intensely purple in ultraviolet light and faded rapidly upon warming. Prolonged irradiation gave irreversibly formation of a photoisomer which is believed to be **19** based on spectral data (Experimental Section) and analogy. Attempted acetylation of the hydroxyl group in **18** gave dark tarry material.



Dihydrodibenzofurans.—In order to assess the effect of the presence or absence of the carbonyl group upon the behavior of these systems, the synthesis of dihydrodibenzofuran derivatives was investigated. Condensation of tetracyanoethylene with 3-benzoyl-2-benzylbenzofuran (**20**)[9] proceeded normally to give the required **21** (Chart III). The corresponding reaction

CHART III



with the isomeric 2-benzoyl-3-benzylbenzofuran (**23**)[9] failed, but the desired product (**25**) was eventually obtained by the photochemical addition method,[2] followed by treatment of the adduct **24** with base.

The hydroxydihydrobenzofurans **21** and **25** did not exhibit photochromism at room temperature, although their pronounced solvatochromism, as had been observed previously with **2** and **4**, demonstrated that thermal ring opening was occurring in polar solvents. Photochemical ring opening was demonstrated by irradiation of **21** and **25** at −196° in glassy hydrocarbon mixtures. Under these conditions the thermal bleaching reaction was inhibited and ultraviolet irradiation produced colored glasses, which upon warming faded rapidly. The fact that **21** and **25** are not photochromic at room temperature is thus presumably due entirely to the fast return rate and not to any lack of photosensitivity.

Acetylation of the hydroxy compounds **21** and **25** readily gave the corresponding acetates, **22** and **26**. Both of the latter compounds were photochromic at 20° in benzene. The pale yellow 1,2-dihydro compound **22** gave a purple solution ($\lambda^{C_6H_6}_{max}$ 553 mμ) upon ultraviolet irradiation, while the isomeric colorless 3,4-dihydro compound **26** gave a blue solution ($\lambda^{C_6H_6}_{max}$ 637 mμ). The colored solutions faded rapidly in the dark; both had decolorized after several seconds at 20°.

The relatively fast fading rates of the colored modifications of the acetates **22** and **26** contrasts markedly with that of the analogous dihydroxanthenone acetate **8**,[2] which upon irradiation gives the isolable colored

(5) B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and H. F. Mower, *J. Amer. Chem. Soc.*, **80**, 2806 (1958).
(6) W. J. Middleton and V. A. Engelhardt, *ibid.*, **80**, 2788 (1958).
(7) K. Wallenfels, G. Bachmann, D. Hofmann, and R. Kern, *Tetrahedron*, **21**, 2239 (1965).
(8) H. Kleinfeller and H. Trommsdorff, *Chem. Ber.*, **71**, 2448 (1938).
(9) K. R. Huffman, M. Loy, and E. F. Ullman, *J. Amer. Chem. Soc.*, **87**, 5417 (1965); **88**, 601 (1966).

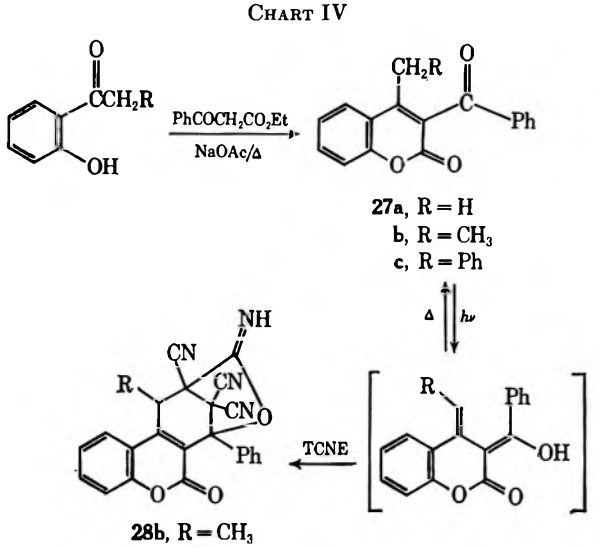
species **9**. Moreover the fading rates of the colored forms of **22** and **26** were found to be substantially accelerated by irradiation with visible light, an effect which also was not observed in the dihydroxanthenone series. Compounds **22** and **26** also seemed to be considerably more stable to prolonged irradiation than tricyanodihydroxanthenones. Although a gradual loss of photochromic activity and formation of permanent color did occur, the frequently observed efficient isomerization to bicyclohexene isomers (*e.g.*, **10**) was not found in the dihydrodibenzofuran series.

3-Benzoyl-4-alkylcoumarins and Their Reactions with Tetracyanoethylene.—A proposed synthesis of dihydrobenzocoumarin analogs of **2** required the preparation of 3-benzoyl-4-alkylcoumarins (**27**). Although 3-benzoyl-4-methylcoumarin (**27a**) has been reportedly obtained in low yield from the thermal condensation of *o*-hydroxyacetophenone with ethyl benzoylacetate,[10] several attempts by us to obtain compounds **27a–c** by this method were unrewarding. Subsequently it was found that addition of a catalytic amount of sodium acetate to the reaction mixture resulted in moderate yields of the desired products.

The photochemistry of the 3-benzoyl-4-alkylcoumarins (**27**) was not studied in detail. Based upon qualitative observations, however, their behavior was similar to that of the isomeric 3-benzoyl-2-alkylchromones (**1**).[9] Thus, the 4-ethyl- and 4-benzyl-3-benzoylcoumarins (**27b** and **c**) underwent photoenolization, as evidenced by color formation and trapping experiments, while the 4-methyl derivative **27a** did not. The pale reddish solutions, formed by irradiation of **27b** and **27c** in hydrocarbon solvents at 25°, faded in a matter of seconds, as opposed to several hours for the corresponding chromones.

Attempted condensation of **27b** and **27c** with tetracyanoethylene, according to the usual technique, employing sodium hydride, was unsuccessful. The difficulty appeared to lie in our inability to generate the coumarin anions. Although irradiation of **27b** and **27c** in the presence of tetracyanoethylene afforded the expected Diels–Alder adducts of the photoenols, in the form of the cyclic imidates **28b** and **28c** (Chart IV),

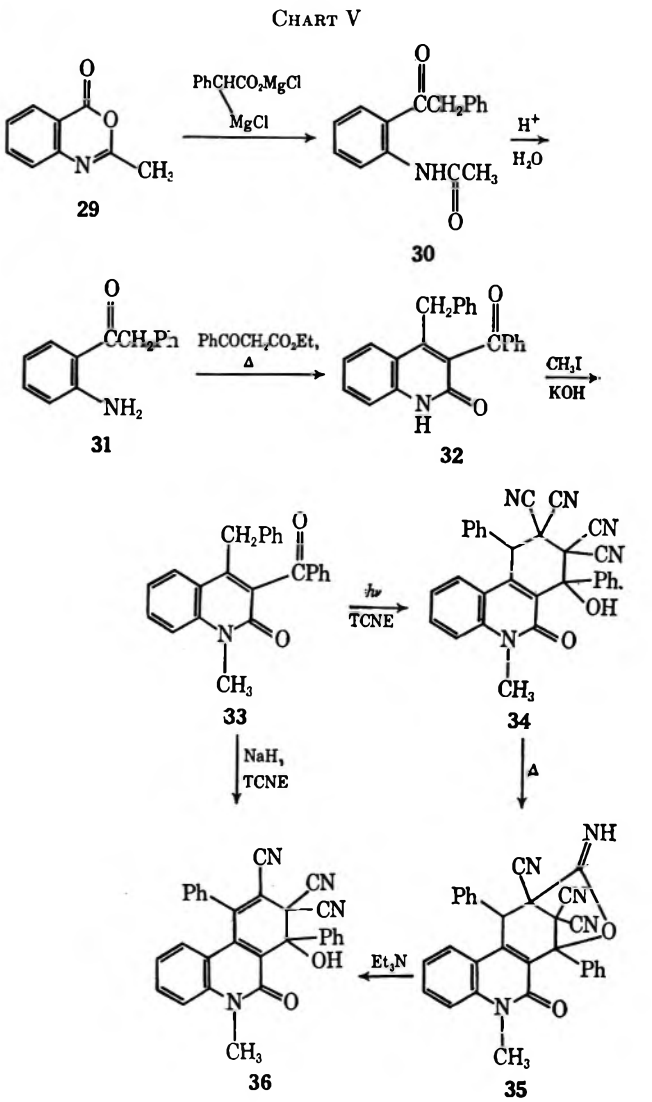
CHART IV



treatment of these adducts with triethylamine according to the method employed previously in the chromone and benzofuran series did not give the desired dihydrobenzocoumarins. The structures of the products of these reactions were not determined.

7,8-Dihydro-6-phenanthridinones.—The preparation of 3-benzoyl-4-benzyl-1-methylcarbostyril (**33**) and its reaction with tetracyanoethylene were also investigated (Chart V). Although the required inter-

CHART V



mediate *o*-amino-*α*-phenylacetophenone (**31**) has been previously reported,[11] its preparation appeared to be lengthy and inconvenient; so an alternate synthesis was achieved through the reaction of acetanthranil (**29**) with the Ivanov reagent[12,13] to give **30** which was then hydrolyzed to **31**. The latter was converted into the carbostyril **32** by the method first used by Camps.[14]

Both **32** and its N-methyl derivative **33** were photochromic in hydrocarbon solvents at room temperature. The pale yellow-orange photoenols produced on irradiation faded within a few seconds after removal from the

(10) D. Molho and J. Brun, *Bull. Soc. Chim. Fr.*, [5] **29**, 1741 (1962).

(11) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 3440 (1953).

(12) An analogous reaction of **29** with benzylmagnesium chloride was previously found to give no isolable amounts of **30**.[13]

(13) W. C. Lothrop and P. A. Goodwin, *J. Amer. Chem. Soc.*, **65**, 363 (1943).

(14) R. Camps, *Arch. Pharm.*, **240**, 135 (1902).

light. By contrast, in the isomeric 3-benzoyl-2-benzyl-4-quinolone series,[9] the N-methyl derivative (**17**) gave an intensely red photoenol which required several hours for complete fading at 25°, while the corresponding nonmethylated 4-quinolone was not photochromic at all.

Condensation of **33** with tetracyanoethylene, using sodium hydride as the base, gave a yellow product believed to be the desired **36** on the basis of analytical and spectral data. The same product was obtained *via* the photoadducts **34** and **35** which were formed by trapping of the photoenol of **33** with tetracyanoethylene. Unexpectedly, the dihydrophenanthridinone **36** was not photochromic when irradiated in a variety of solvents at temperatures from 25 to −196°, although some photochemical reaction did occur as evidenced by changes in the ultraviolet spectrum. Like its isomer **18**, compound **36** exhibited only a weak solvatochromism (Table II).

Inasmuch as **18** was photochromic only in fluid solutions at low temperature (<−50°) and not in low temperature glasses, a slight increase in the return rate of **36** over that of **18** might explain the lack of observable photochromism in **36**. Within the present series of cyano-substituted cyclohexadienes **36** is the only example which was not photochromic under any set of conditions.

Photochromic Behavior.—The results of quantitative determinations of the efficiencies of the color forming reactions and the rates of the thermal fading processes are presented in Table IV. Omitted from the table are compounds which were photochromic only at low temperatures (**18, 21,** and **25**) and the imide derivatives **12, 15,** and **16,** which were not studied in detail. The tricyanodihydroxanthenones **2a** and **8** are included for the purpose of comparison. Table IV also gives qualitative results of irradiation of these compounds in glassy hydrocarbon mixtures at −196°.

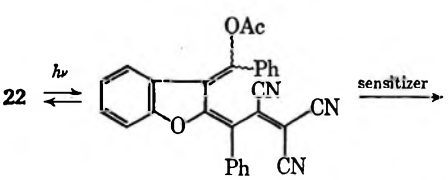
Significantly slower thermal fading rates were found in the dicyanodihydroxanthenone series compared with the corresponding tricyano derivatives. Comparison of molecular models of **3** and **5** shows that the extra cyano group present in **3** contributes greatly to the steric repulsions in this system and provides a greater driving force for cyclization to the unstrained colorless forms.

The reasons for the substantial increase in the thermal fading rates upon passing from the tricyanodihydroxanthenones to the tricyanodihydrodibenzofurans are less obvious. Since a large rate difference is observed not only between the hydroxy compounds of each class but also between the acetates (compare **2a** with **21** and **25**; **8** with **22** and **26**), it is doubtful if the hydrogen bonding available in the hydroxytriene **3a** is the primary cause of its increased stability relative to the colored modifications of **21** and **25**. Rather it appears that the rapid fading of the dihydrodibenzofuran derivatives may be related to the size of the heteroring which controls the angle between the two exocyclic double bonds in the colored forms and thus can affect the stereochemical interactions in the system. The greater bond angle between the exocyclic double bonds of the colored forms of the dihydrodibenzofurans, compared with the dihydroxanthenones, results in less steric crowding in the former and thereby facilitates conversion into the all-*cis* conformation required for both thermal and photochemical cyclization.

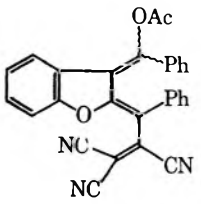
The results obtained upon low-temperature irradiation of the cyclohexadienes were generally similar to those observed previously in the tricyanodihydroxanthenone series.[2b,4] Thus irradiation of the hydroxydicyano derivatives **4** at −196° afforded colored glasses containing labile triene intermediates which were converted into the more stable triene forms **5** upon warming and which were readily bleached, while cold, upon irradiation with visible light. The colored species (**5**) obtained at room temperature did not readily photobleach. As discussed previously[2b] the low-temperature intermediates are believed to correspond to an all-*cis* conformation observable only in rigid media under conditions not allowing conversion into alternative lower energy conformations. Since the acetates **6** and the dihydroacridone **18** were photosensitive only in fluid solution, the related intermediates could not be observed in these instances.

The acetoxydihydrodibenzofurans **22** and **26** also afforded low temperature intermediates absorbing at longer wavelengths than the room temperature colored forms. In these cases both the colored species obtained at −196° and those formed by irradiation near room temperature were rapidly photobleached with visible light. However, if the colored solutions resulting from the room temperature irradiation were subsequently frozen at −196°, they were no longer sensitive to visible irradiation. Quite probably the photosensitive species are all-*cis* trienes (at −196°) or have all-*cis* conformations in equilibrium (at 20°) whereas the light-insensitive species resulting from cooling of the colored solutions are non-all-*cis* conformations (*e.g.*, **37**) which can not change in the frozen rigid medium.

Interestingly, **22**, which has no carbonyl group, behaved differently with sensitizers than the carbonyl-containing dihydroxanthenone derivatives **2a** and **8**. While the latter compounds both became colored during irradiation with benzophenone or thioxanthone in benzene, the benzofuran **22** remained colorless. If an amount of sensitizer was used that was insufficient to absorb all the light, then solutions of **22** very gradually turned blue. However, this color differed from the color produced upon direct irradiation, not only in hue but also in its greater thermal and light stability compared with the "normal" color. This result is most readily interpreted by assuming that the original color-forming process occurs solely by light absorbed directly by **22**, and that the initially formed "normal" colored modification **37** undergoes a photosensitized reaction to give the geometrical isomer **38**. The latter might then



37



38

owe its higher thermal and photochemical stability to its inability to undergo cyclization to **22** without prior *cis–trans* isomerization.

Experimental Section

All preparative photochemical reactions were performed in quartz or Vycor vessels using a 1000-W General Electric B-H6 high-pressure mercury arc equipped with a Corning No. 9863 nickel oxide filter, transmitting approximately 240–400-mμ light. The qualitative photochromic tests were performed in Pyrex glass tubes using the same lamp and filter combination. Visible light was obtained from a 500-W Argus No. 540 slide projector fitted with a Corning No. 3387 filter transmitting at >430 mμ. The rate and quantum yield measurements were carried out as described previously.[2b]

2-Benzyl-3-(*p*-methoxybenzoyl)chromone (1c) was prepared in 32% yield by the reaction of *o*-hydroxy-*p'*-methoxydibenzoylmethane[15] with phenylacetic anhydride, according to the general procedure of ref 9. It was obtained as colorless crystals, mp 143–144.5°, from ethanol.

Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.82; H, 4.90. Found: C, 77.95; H, 4.87.

2-Ethyl-3-(*p*-methoxybenzoyl)chromone (1e).—A similar reaction using propionic anhydride afforded a 64% yield of **1e** as colorless crystals, mp 100–101°, from hexane.

Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.70; H, 5.25.

3-Benzoyl-4-methylcoumarin (27a).—A mixture of 6.8 g of *o*-hydroxyacetophenone (0.05 mol), 9.6 g of ethyl benzoylacetate (0.05 mol), and 100 mg of sodium acetate was heated at 210–220° under nitrogen for 2.5 hr. The cooled reaction mixture was treated with 100 ml of 5% aqueous sodium hydroxide and extracted three times with a 2:1 ether–methylene chloride mixture. The dried extracts were evaporated and the oily residue was crystallized from ether–petroleum ether to give 4.35 g (33%) of tan crystals, mp 139–140.5°. Two recrystallizations from ethanol afforded colorless crystals, mp 140.5–141.5° (lit.[10] mp 143°).

3-Benzoyl-4-ethylcoumarin (27b).—The above procedure was repeated using *o*-hydroxypropiophenone. The coumarin **27b** was obtained in 28% yield, mp 108.5–112.5°. Two recrystallizations from ethanol gave colorless prisms, mp 113–114°.

Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.54; H, 5.20.

3-Benzoyl-4-benzylcoumarin (27c).—The above procedure was applied to a mixture of 1.87 g of *o*-hydroxy-α-phenylacetophenone,[16,17] 1.70 g of ethyl benzoylacetate, and 50 mg of sodium acetate. The yield of **27c** was 0.91 g (30%), mp 122.5–126.5°. After recrystallization from ethanol, the analytical sample had mp 127.5–128.5°.

Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.16; H, 4.74. Found: C, 81.01; H, 4.97.

2'-(Phenylacetyl)acetanilide (30).—The Ivanov reagent was prepared by dropwise addition of a solution of 17.5 g of phenylacetic acid (0.13 mol) in 135 ml of benzene to a stirred solution of isopropylmagnesium chloride (from 7.0 g of magnesium and 24.5 g of isopropyl chloride) in 200 ml of ether.[18] The mixture was stirred overnight and then 18.9 g (0.117 mol) of 2-methyl-3,1-benzoxazin-4-one[19] (**29**) was added as a solid in portions. The reaction mixture was refluxed with stirring for 6 hr and treated with ice and concentrated hydrochloric acid. The organic layer was separated, washed with 5% sodium bicarbonate, dried, and evaporated. Recrystallization of the resulting solid from petroleum ether gave 8.4 g (28%) of **30** as a white solid, mp 98–100° (lit.[11] mp 97–98°).

σ-Amino-α-phenylacetophenone (31).—The above N-acetyl compound was hydrolyzed according to the literature procedure[11] to give a 95% yield of **31**, mp 101–103°. The reported[11] mp is 103–104°.

3-Benzoyl-4-benzylcarbostyril (32).—A mixture of 1.0 g of σ-amino-α-phenylacetophenone and 0.92 g of ethyl benzoylacetate was heated at 175° for 45 min under nitrogen. The resulting solid was washed with ether and recrystallized from ethanol to give 1.24 g (77%) of **32**, mp 262–265°. A second recrystallization from methanol afforded colorless plates, mp 263.5–265.5°.

Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13. Found: C, 81.17; H, 4.80; N, 4.08.

3-Benzoyl-4-benzyl-1-methylcarbostyril (33).—To a solution of 10.9 g (0.19 mol) of potassium hydroxide in 350 ml of methanol was added 6.6 g (0.019 mol) of 3-benzoyl-4-benzylcarbostyril and 27.6 g (0.19 mol) of methyl iodide. The mixture was refluxed for 6 hr and evaporated to dryness. The residue was washed with water and crystallized from ethanol to give 5.4 g (78%) of colorless crystals of **33**, mp 176.5–179°. One further recrystallization raised the melting point to 178–179°.

Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.47; H, 5.34; N, 4.01.

Preparation of 1,2-Dihydroxanthenones and Related Compounds. General Procedure.—The following general procedure is illustrative of the preparation of compounds **4a–e**, **12**, **18**, **21**, and **36**. Analytical and melting point data are listed in Table I, along with yields and reaction times.

To a stirred suspension of 1.0 g (0.020 mol) of sodium hydride (50% dispersion in mineral oil) in 25 ml of dry tetrahydrofuran under nitrogen was added dropwise a solution of 0.015 mol of the *vic*-alkylaroyl heterocycle in the minimum amount of dry tetrahydrofuran. The mixture became deeply colored as hydrogen was evolved and the anion formed. After the addition was complete the mixture was refluxed with stirring for 10 min, then cooled to 25° and treated dropwise with a solution of 0.016 mol of the olefin component (tetracyanoethylene, methoxymethylenemalononitrile,[20] or 2-chloro-3-cyanomaleimide[21]) in tetrahydrofuran. The resulting mixture was stirred at reflux for 1–6 hr and evaporated to dryness *in vacuo*. The residual gum or solid was taken up in ice water and washed twice with ether or methylene chloride to remove the mineral oil and any unreacted starting materials. The aqueous solution was then acidified and extracted several times with methylene chloride. The combined extracts were dried and evaporated to give a gum or solid which was crystallized by trituration with an appropriate solvent and then purified by recrystallization from methylene chloride–petroleum ether.

2,3-Dibenzoyl-1,4-diphenyl-9-xanthenone (11).—Condensation of 0.34 g of 3-benzoyl-2-benzylchromone (**1a**) with chlorotribenzoylethylene[8] according to the above procedure afforded a water-insoluble orange solid which was triturated with boiling ethanol to give 0.33 g of **11**, mp 232–234°. A second crop of 0.12 g, mp 219–224°, was obtained by addition of water to the filtrate. The total yield of unrecrystallized material was 0.45 g (80%). Two recrystallizations from ethanol gave pale yellow crystals, mp 233–234°.

Anal. Calcd for $C_{39}H_{24}O_4$: C, 84.16; H, 4.35. Found: C, 83.90; H, 4.26.

Photoaddition of Tetracyanoethylene to 2-Benzoyl-3-benzylbenzofuran.—A stirred solution of 0.31 g of 2-benzoyl-3-benzylbenzofuran (**23**) and 0.13 g of tetracyanoethylene in 15 ml of ethyl acetate contained in a water-jacketed quartz vessel under nitrogen was irradiated with 240–400-mμ light from the B-H6 lamp. After 7 hr the solution was evaporated and the residue was crystallized from ether–petroleum ether to give 0.34 g (77%) of the photoadduct **24**, mp 176–180° dec. Three recrystallizations from methylene chloride–petroleum ether afforded pale yellow crystals: mp 190–192° dec; λ_{max}^{mull} 3.04 (N—H), 5.85 μ (C=N).

Anal. Calcd for $C_{28}H_{16}N_4O_2$: C, 76.36; H, 3.66; N, 12.72. Found: C, 75.83; H, 3.67; N, 12.77.

Photoaddition of Tetracyanoethylene to 3-Benzoyl-4-ethylcoumarin (27b).—The adduct **28b** was obtained in 20% yield as colorless crystals, mp >220° dec, from ethanol, after 18 hr irradiation according to the above procedure. It showed λ_{max}^{mull} 3.04, 5.78, and 5.81 μ.

Anal. Calcd for $C_{24}H_{14}N_4O_3$: C, 70.93; H, 3.47; N, 13.79. Found: C, 70.74; H, 3.37; N, 13.61.

Photoadduct of Tetracyanoethylene and 3-Benzoyl-4-benzylcoumarin.—Irradiation of **27c** and tetracyanoethylene in ethyl acetate for 18 hr afforded a mixture of products from which **28c** was separated by fractional crystallization from ethanol. Recrystallization from acetonitrile afforded a 15% yield of solvated **28c**: mp >275° dec; λ_{max}^{mull} 3.0, 5.67, and 5.82 μ.

(15) W. Baker and F. Glockling, *J. Chem. Soc.*, 2759 (1950).
(16) J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.*, **34**, 155 (1957).
(17) M. O. Farooq, W. Rahman, M. Ilyas, and S. Jehan, *Chem. Ber.*, **94**, 1996 (1961).
(18) *Cf.* F. F. Blicke and S. Raines, *J. Org. Chem.*, **29**, 204 (1964).
(19) M. T. Bogert and H. A. Seil, *J. Amer. Chem. Soc.*, **29**, 517 (1907).
(20) A. Ishiwata, *Takamine Kenkyusho Nempo*, **9**, 21 (1957); *Chem. Abstr.*, **55**, 1439 (1961).
(21) R. H. Wiley and S. C. Slaymaker, *J. Amer. Chem. Soc.*, **80**, 1385 (1958).

Anal. Calcd for $C_{29}H_{16}N_4O_3 \cdot CH_3CN$: C, 73.08; H, 3.76; N, 13.74. Found: C, 73.09; H, 3.79; N, 13.42.

Photoaddition of Tetracyanoethylene to 3-Benzoyl-4-benzyl-1-methylcarbostyril.—A solution of 707 mg of **33** and 256 mg of tetracyanoethylene in 60 ml of ethyl acetate was irradiated for 16 hr as above. The solvent was removed and the residue was crystallized from ether. **7,10-Diphenyl-7-hydroxy-5-methyl-8,8,-9,9-tetracyano-7,8,9,10-tetrahydro-6-phenanthridinone (34)** was obtained as a gray solid: 157 mg (16%); mp 202.5–204° dec; λ_{max}^{mull} 3.10, 6.12 μ.

Anal. Calcd for $C_{30}H_{19}N_5O_2$: C, 74.83; H, 3.98; N, 14.55. Found: C, 74.53; H, 4.32; N, 14.20.

The above adduct, when recrystallized from boiling ethanol, was converted into the cyclic imidate **35**: mp 238–240° dec; λ_{max}^{mull} 3.05, 5.80, 6.08 μ.

Anal. Calcd for $C_{30}H_{19}N_5O_2$: C, 74.83; H, 3.98; N, 14.55. Found: C, 74.54; H, 4.25; N, 14.64.

By reaction with triethylamine in tetrahydrofuran at 25° for 2 days compound **35** was converted into **7,8-dihydro-7,10-diphenyl-7-hydroxy-5-methyl-6-phenanthridinone (36)** which was identical with the sample prepared by direct condensation of **33** with tetracyanoethylene (Tables I and II, and earlier procedure).

3,4-Dihydro-1,4-diphenyl-4-hydroxy-2,3,3-tricyanodibenzofuran (25).—A solution of 0.27 g of the imidate **24** in 10 ml of tetrahydrofuran was treated with a few drops of triethylamine and allowed to stand overnight. The resulting purple gum was partitioned between ether and 5 *N* hydrochloric acid, which caused the color to fade. The ether layer was separated and combined with ethereal extracts of the aqueous layer. The dried extracts were evaporated and the resulting solid was recrystallized twice from ether–petroleum ether (bp 30–60°) to give 0.18 g (60%) of **25** as colorless crystals, mp 108.5–110.5° dec.

Anal. Calcd for $C_{27}H_{15}N_3O_2 \cdot C_4H_{10}O$ (ether solvate): C, 76.37; H, 5.17; N, 8.62. Found: C, 76.31; H, 4.96; N, 8.59.

Acetylation of Hydroxydihydroxanthenones and Hydroxydihydrodibenzofurans.—The following general procedure was used in the preparation of compounds **6a, 6d, 15, 22** and **26**. Yields, melting points, and analytical data are given in Table III.

A solution of 1 g of the hydroxy compound in the minimum amount of acetic anhydride was treated with 3 drops of concentrated sulfuric acid and kept at room temperature for 1–2 hr. The solution was then poured into ice water and the resulting mixture was stirred until crystallization of the product was complete. The product was filtered, washed with water, and recrystallized from ethanol or methylene chloride–petroleum ether.

Photolysis of 1-Acetoxy-2,2-dicyano-1,2-dihydro-4-methyl-1-phenyl-9-xanthenone.—A solution of 30 mg of **6d** in 20 ml of benzene in a Vycor flask was irradiated for 4 hr with the B-H6 lamp using a Corning No. 9863 filter. The resulting red solution was evaporated and the product was recrystallized from benzene–heptane giving the triene **7d** as purple-black crystals: mp 181–183°; λ_{max}^{mull} 4.54, 5.67, and 6.00 μ; $\lambda_{max}^{CH_2Cl_2}$ 251 (4.34) 295 sh (4.04), 372 sh (4.04), and 463 mμ (log ϵ 4.34).

Anal. Calcd for $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07. Found: C, 72.77; H, 4.17.

2-Cyano-1,2-dihydro-1,4-diphenyl-1-hydroxy-9-xanthenone-2,3-(N-methyldicarboximide) (16).—A solution of 0.48 g of **12** in 25 ml of dry tetrahydrofuran was added dropwise with stirring to a suspension of 0.20 g of 50% sodium hydride (4.0 equiv) in 5 ml of tetrahydrofuran. The purple mixture was refluxed with stirring for 10 min giving an intensely blue solution. A 20-fold excess, 2.8 g of methyl iodide was added and refluxing was continued for 1.5 hr while the color gradually reverted to the original purple. The cooled solution was treated with wet tetrahydrofuran to decompose the excess sodium hydride and then evaporated to dryness. An aqueous solution of the residue was washed with methylene chloride and then acidified with dilute hydrochloric acid. The dark oil was extracted from the aqueous mixture with several portions of methylene chloride and crystallized from methylene chloride–petroleum ether. The product **16** was obtained as tan crystals: mp 177–180° dec; 0.26 g (46%); λ_{max}^{mull} 3.08, 4.45, 5.63, 5.85, 6.08, and 6.17 μ.

Anal. Calcd for $C_{29}H_{18}N_2O_5 \cdot CH_2Cl_2$: C, 64.41; H, 3.60; N, 5.01. Found: C, 64.26; H, 3.50; N, 5.17.

Photolysis of 2-Cyano-1,2-dihydro-1,4-diphenyl-1-hydroxy-9-xanthenone-2,3-dicarboximide.—A solution of 150 mg of **12** in 40 ml of methylene chloride in a Vycor flask was flushed with nitrogen, stoppered, and stirred for 14 hr while irradiating with the B-H6 lamp equipped with a Corning No. 9863 filter. The solution was concentrated and diluted with petroleum ether yielding 75 mg (50%) of tan crystals of **14**, mp 231.5–232.5° dec. Two recrystallizations from ethanol–water gave material of mp 237–239° dec; λ_{max}^{mull} 2.94, 3.60, 4.42, 5.61, 5.81, 6.10, and 6.21 μ; $\lambda_{max}^{CH_2Cl_2}$ 242 (4.40), 272 sh (3.93), and 300 mμ (log ϵ 3.93).

Anal. Calcd for $C_{28}H_{16}N_2O_5$: C, 73.04; H, 3.50; N, 6.08. Found: C, 72.75; H, 3.49; N, 5.92.

Photolysis of 1,2-Dihydro-1,4-diphenyl-1-hydroxy-10-methyl-2,2,3-tricyano-9-acridone.—A solution of 100 mg of **18** in methylene chloride was irradiated for 6 hr under the conditions described in the preceding example. The photoisomer **19** was obtained as tan crystals: mp 238–240° dec; λ_{max}^{mull} 2.95, 4.45, 6.20, and 6.30 μ; $\lambda_{max}^{CH_2Cl_2}$ 249 (4.35), 283 (3.57), 298 (3.52), 330 (3.99), and 343 mμ (log ϵ 4.02).

Anal. Calcd for $C_{29}H_{18}N_4O_2 \cdot 0.5H_2O$: C, 75.15; H, 4.13; N, 12.09. Found: C, 75.22; H, 4.07; N, 11.92.

Registry No.—**1c**, 19981-84-1; **1e**, 19981-85-2; **2a**, 13562-55-5; **4a**, 13562-62-4; **4b**, 19981-88-5; **4c**, 19981-89-6; **4d**, 19981-90-9; **4e**, 19981-91-0; **6a**, 13562-64-6; **6d**, 19981-93-2; **7d**, 19987-95-2; **8**, 15725-91-4; **11**, 19987-74-7; **12**, 19987-75-8; **14**, 19987-76-9; **15**, 19987-77-0; **16**, 19987-78-1; **18**, 13562-59-9; **19**, 20013-30-3; **21**, 13562-60-2; **22**, 13562-63-5; **24**, 14724-83-5; **25**, 13620-51-4; **26**, 13620-52-5; **27b**, 19988-00-2; **27c**, 19988-01-3; **28b**, 19988-02-4; **28c**, 19988-03-5; **30**, 19988-04-6; **32**, 19988-05-7; **33**, 19988-06-8; **34**, 19988-07-9; **35**, 19988-08-0; **36**, 19988-09-1.

Neighboring-Group Study in Solvolyses of Cyclopentyl and Cyclohexyl Tosylates

DONALD D. ROBERTS AND WILLIAM HENDRICKSON[1]

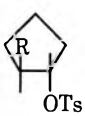
Department of Chemistry, Louisiana Polytechnic Institute, Ruston, Louisiana 71270

Received November 18, 1968

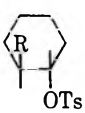
Solvolysis rates of cyclopentyl (5-H), cyclohexyl (6-H), *trans*-2-trifluoroacetoxycyclopentyl (5-OTf), *trans*-2-trifluoroacetoxycyclohexyl (6-OTf), *trans*-2-methoxycyclopentyl (5-OMe), *trans*-2-methoxycyclohexyl (6-OMe), *trans*-2-chlorocyclopentyl (5-Cl), and *trans*-2-chlorocyclohexyl (6-Cl) tosylates have been determined in acetic, formic, and trifluoroacetic acids. The neighboring trifluoroacetoxy substituent effect upon the rates of solvolysis is sensitive to reaction medium. In contrast, both the neighboring methoxy and chloro substituent effects upon the rates of solvolysis are insensitive to reaction medium. The implications of this solvolytic behavior is discussed in terms of solvent influence upon the opposing participation and inductive effects of the investigated neighboring groups.

The rates of solvolysis of a series of *trans*-2-hydroxycycloalkyl tosylates have recently been reported.[2,3] Based upon electrostatic considerations,[4] and the application of Taft's equation to polar effects in acetolyses,[5] a 10^{-2} rate-retarding influence upon SN1-type reactions was predicted for the neighboring *trans*-hydroxy substituent. Contrary to this expectation, it was found that the order of the expected rate retardation was greatly reduced in aqueous alcohol and acetic acid solvents, and was approached only in formic acid. The solvent dependency of this neighboring-group effect on the reaction rate was rationalized in terms of solvent influence upon the opposing participation and inductive effects of the *trans*-2-hydroxy substituent.

Prompted by these results, we were encouraged to extend this neighboring-group study to other substituents and also to increase the range of solvent ionizing strength.[6] Accordingly, this Article reports the kinetic investigations of the solvolytic reactions of cyclopentyl (5-H), *trans*-2-trifluoroacetoxycyclopentyl (5-OTf), *trans*-2-methoxycyclopentyl (5-OMe), *trans*-2-chlorocyclopentyl (5-Cl), cyclohexyl (6-H), *trans*-2-trifluoroacetoxycyclohexyl (6-OTf), *trans*-2-methoxycyclohexyl (6-OMe), and *trans*-2-chlorocyclohexyl (6-Cl) tosylates in trifluoroacetic acid. Since the sensitivity of the rates



5-H, R = H
5-OTf, R = O_2CCF_3
5-OMe, R = OMe
5-Cl, R = Cl



6-H, R = H
6-OTf, R = O_2CCF_3
6-OMe, R = OMe
6-Cl, R = Cl

of limiting-type[6] solvolyses to neighboring-group effects is significantly enhanced in trifluoroacetic acid,[7,8] a kinetic investigation of the trifluoroacetolyses of the above compounds is of particular interest in the study of solvent influence upon such effects.

The first-order rate constants for the trifluoroacetolysis of 5-H through 5-Cl and 6-H through 6-Cl are given in Table I. In addition, the rate constants for the formolysis and acetolysis of selected substrates are reported.[9] The solvolysis rates of the reactions in trifluoroacetic and formic acid were measured spectrophotometrically using the method developed by Peterson, *et al.*[10] while the acetolysis reactions were followed titrimetrically.[2] The solvolysis reactions of 6-OTf in trifluoroacetic acid gave clean first-order plots over only 15% reaction. Absorption curves for longer times showed steadily increasing absorbance indicating the formation of interfering side product(s). The rate constant listed for the trifluoroacetolysis of 6-OTf is an average of six runs and is considered to be a maximal value. All of the other reactions exhibited first-order behavior through at least 75% conversion. The slower acetolysis reactions were followed to 20–30% conversion.

Results and Discussion

Although the degree of SN1 character for the acetolysis of secondary tosylates may be open to discussion,[7] the evidence supporting a limiting-type solvolysis for secondary tosylates in formic and trifluoroacetic acids is strong.[7,8,10] Previously, it was observed[3] that the values of k_5/k_6, the ratio of solvolysis of 5-H to that of 6-H, varied in a series of solvents from 27 (in ethanol) to 8.4 (in formic acid). This decrease in the relative rate (k_5/k_6) with decreasing nucleophilic strength[6] of the solvent was interpreted by a parallel decrease in the nucleophilic contribution of the solvent to the transition state. Consistent with this interpretation is the observation that the values of k_5/k_6 are quite similar in weakly nucleophilic, strongly ionizing[8] formic (8.4) and trifluoroacetic (7.2) acids.

Examination of the k^X/k^H ratios listed in Table II reveals that the neighboring trifluoroacetoxy substituent demonstrates a significant response to the medium change; the rate-retarding inductive effect is 20–30 times greater in trifluoroacetic acid than in acetic acid. Enhancement of the trifluoroacetoxy inductive effect in trifluoroacetolyses relative to acetolyses is in accord with the increased solvent hydrogen-bonding ability of trifluoroacetic acid. This explanation has been ad-

(1) Undergraduate research assistant.
(2) D. D. Roberts and J. G. Traynham, *J. Org. Chem.*, **32**, 3177 (1967).
(3) D. D. Roberts, *ibid.*, **33**, 118 (1968).
(4) S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 828 (1948).
(5) A. Streitwieser, Jr., *ibid.*, **78**, 4935 (1956).
(6) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 63–65.
(7) P. E. Peterson, R. J. Ropp, D. M. Chevli, E. L. Curran, D. E. Dillard, and R. J. Kamat, *J. Amer. Chem. Soc.*, **89**, 5902 (1967).
(8) J. E. Nordlander and W. G. Deadman, *ibid.*, **90**, 1590 (1968).
(9) Originally, the trifluoroacetolysis of *trans*-2-hydroxycyclopentyl (5-OH) and *trans*-2-hydroxycyclohexyl (6-OH) tosylates were included; however, it was found that 70% of 5-OH was converted into 5-OTf before 10% of the *p*-toluenesulfonic acid was liberated and that *ca.* 100% of 6-OH was converted into 6-OTf before 2% of the acid was liberated.
(10) P. E. Peterson, R. F. Kelley, Jr., R. Belloli, and K. A. Sipp, *ibid.*, **87**, 5169 (1965).

TABLE I
FIRST-ORDER SOLVOLYSIS RATES

Tosylate[a]	Solvent	Temp, °C	k_1,[b] sec^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
Cyclopentyl	CF_3CO_2H	0	2.0×10^{-4}	15.6	−18
		10	5.6×10^{-4}		
		15	9.2×10^{-4}		
		20	15.3×10^{-4}		
trans-2-Trifluoroacetoxycyclopentyl	CF_3CO_2H	50	5.5×10^{-6}		
		70	3.3×10^{-5}		
	HCO_2H	70	1.6×10^{-5}		
	CH_3CO_2H	70	1.8×10^{-6}		
trans-2-Methoxycyclopentyl	CF_3CO_2H	40	3.26×10^{-5}	22.6	−7
		50	10.0×10^{-5}		
		70	84.9×10^{-5}		
	HCO_2H	45	1.9×10^{-5}		
	CH_3CO_2H	45	8.6×10^{-8}		
trans-2-Chlorocyclopentyl	CF_3CO_2H	40	3.38×10^{-5}	15.4	−30
		45	5.0×10^{-5}		
		70	32.0×10^{-5}		
	CH_3CO_2H	70	2.8×10^{-7}		
Cyclohexyl	CF_3CO_2H	25	2.7×10^{-4}	18.5	−13
		30	4.3×10^{-4}		
		40	13.1×10^{-4}		
		45	21.0×10^{-4}		
		50	30.6×10^{-4}		
trans-2-Trifluoroacetoxycyclohexyl	CF_3CO_2H	45	4.0×10^{-7}		
	HCO_2H	70	28.0×10^{-7}		
	CH_3CO_2H	70	7.2×10^{-8}		
trans-2-Methoxycyclohexyl	CF_3CO_2H	30	4.1×10^{-6}	23.2	−6
		50	58.2×10^{-6}		
		70	434×10^{-6}		
	HCO_2H	45	1.3×10^{-5}		
	CH_3CO_2H	45	2.6×10^{-8}		
trans-2-Chlorocyclohexyl	CF_3CO_2H	40	2.63×10^{-6}	17.9	−28
		50	4.63×10^{-6}		
		70	35.6×10^{-6}		
	CH_3CO_2H	70	1.0×10^{-8}		

[a] Initial concentrations 0.30–0.050 and 0.125 *M* in sodium trifluoroacetate for the trifluoroacetolyses. [b] The standard deviation of these rate constants ranged from ±0.5 to ±4.0%.

TABLE II
COMPARISON OF REACTION RATES OF *trans*-2-X-CYCLOALKYL AND CYCLOALKYL TOSYLATES IN VARIOUS SOLVENTS

Solvent	k^X/k^H CF_3CO_2	CH_3O	Cl
Five-Membered-Ring Compounds			
AcOH	0.004[a]	0.004[b]	0.001[a]
HCO_2H	0.0003[a]	0.004[b]	
CF_3CO_2H	0.0003[a]	0.004[b]	0.002[b]
Six-Membered-Ring Compounds			
AcOH	0.003[a]	0.01[b]	0.002[a]
HCO_2H	0.0003[a]	0.02[b]	
CF_3CO_2H	0.0001[b]	0.01[b]	0.002[b]

[a] At 70°. [b] At 45°.

vanced by Peterson[11] to explain the large rate decreases in addition reactions of trifluoroacetic acid to 5-substituted 1-hexenes and by Taft[12] to explain the effects of solvent on the shielding parameter of *meta*-substituted fluorobenzenes with oxygen- and nitrogen-containing substituents.

In contrast to the solvent sensitive effect of the trifluoroacetoxy group in the solvolysis reactions of 5-OTf and 6-OTf, the effect of the methoxy neighboring group is insensitive to the solvent change in the solvolysis reactions of 5-OMe and 6-OMe. In fact, in all solvents investigated the magnitude of k^{OMe}/k^H is close to the predicted[4] value of 10^{-2} based purely on electrostatic considerations. Similarly, the effect of the chloro substituent is nearly insensitive to the medium change; the value of k^{Cl}/k^H is *ca.* 10^{-3} in both acetic and trifluoroacetic acids.

Although the substituent–solvent interaction for halo groups is small,[12] an enhanced rate retardation is to be expected for the trifluoroacetolysis of 5-Cl or 6-Cl owing to enhanced charge development in the transition state.[13] The fact that the substituent effect is invariant with the solvent change suggests that the predominantly rate-retarding inductive effect of the chloro group is partially compensated by neighboring-group assistance in trifluoroacetic acid and to a much lesser extent in formic acid. This suggestion is supported by the demonstrated ability of trifluoroacetic acid to promote both significant phenyl neighboring-group assistance in the solvolysis of 2-phenylethyl tosylate[8] and significant participation by the chloro group in the solvolysis of 5-chloro-2-hexyl tosylate.[7]

The apparent lack of solvent dependence of the methoxy neighboring-group effect is also understandable

(11) P. E. Peterson and G. Allen, *J. Amer. Chem. Soc.*, **85**, 3608 (1963).
(12) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *ibid.*, **85**, 709 (1963).
(13) This argument is based on a generally accepted postulate of carbonium ion theory, *i.e.*, the faster an SN1-type reaction, the more ionic its transition state. For a recent discussion, see H. M. R. Hoffmann, *J. Chem. Soc.*, 6762 (1965).

in terms of a predominantly rate-retarding inductive effect partially compensated by methoxy participation in the ionization process; however, supperimposed on these effects is the possible presence of steric inhibition of solvation. Examination of the models of the carbonium ionlike transition state for the solvolysis of **5**-OMe and **6**-OMe suggests that steric interactions between the methoxy substituent and the ring hydrogens are minimized when the methoxy group is twisted out of the ring as illustrated in Figure 1. In the representation for **6**-OMe, the methoxy substituent is pictured in the stereoelectronically more favorable axial position.[14] In these particular conformations, hydrogen bonding of the methoxy group by the solvent molecules would introduce sufficient steric crowding to minimize the difference in hydrogen-bonding ability among the three solvents.

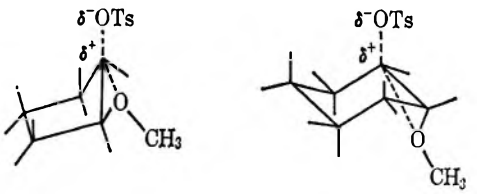


Figure 1.

Experimental Section

Melting and boiling points were not corrected for stem exposure. The former were taken on a Mel-Temp apparatus. Spectra were determined on a Perkin-Elmer Model 21 spectrophotometer. An F & M Model 700 gas chromatograph equipped with a hydrogen-flame detector and a 6-ft column of 10% Carbowax 20M on Celite was used for analytical vpc work. All microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Cyclopentyl tosylate (**5**-H) was prepared in 55% yield by the previously published procedure,[3] mp 29.0–29.5° (lit.[15] mp 29.1°).

trans-**2-Methoxycyclopentanol.**—A mixture of 21.0 g (0.25 mol) of cyclopentene oxide, 100 ml of anhydrous methanol, and 2 drops of concentrated sulfuric acid was held under reflux for 8 hr. The acid was then neutralized with barium carbonate and the mixture filtered. Distillation of the filtrate gave 11.5 g (40% yield) of product: bp 80° (10 mm); n^{25}D 1.4515 [lit.[16] bp 96° (27 mm); $n^{25.2}$D 1.4513]. Gc analysis indicated minimum purity of 99%.

trans-**2-Methoxycyclopentyl tosylate** (**5**-OMe) was prepared in 60% yield by standard procedure.[3] The crude ester was purified three times by precipitation from petroleum ether (bp 30–60°) at Dry Ice–acetone temperature. The final traces of solvent were removed by flash distillation under reduced pressure (*ca.* 0.1 mm) to yield an oil of greater than 97% purity by infinity absorbance: ir (neat), 1335 (ν_{SO_2} asymmetric), 1165 (ν_{SO_2} symmetric), and 1090 cm^{-1} (ether COC).

trans-**2-Chlorocyclopentanol** was prepared in 80% yield by passing dry HCl into a solution of 150 g of cyclopentene oxide in 150 ml of carbon tetrachloride until the solution was saturated. The solution was then washed with water, sodium bicarbonate solution, and water, dried over magnesium sulfate, and distilled to give the product: bp 81–82° (15 mm); n^{25}D 1.4775 [lit.[17] bp 81–82° (15 mm); n^{35}D 1.4770].

trans-**2-Chlorocyclopentyl tosylate** (**5**-Cl) was prepared in 72% yield by standard procedure.[3] Four recrystallizations from petroleum ether (bp 30–60°)–benzene gave the analytical sample of the ester, mp 38–39°.

Anal. Calcd for $C_{12}H_{15}ClO_3S$: C, 52.46; H, 5.50; Cl, 12.90. Found: C, 52.65; H, 5.54; Cl, 13.09.

trans-**2-Trifluoroacetorycyclopentyl Tosylate** (**5**-OTf).—To a cold solution of *trans*-2-hydroxycyclopentyl tosylate[3] (2 g, 7.5 mmol) in 10 ml of dry pyridine was cautiously added 1.32 g (10 mmol) of trifluoroacetyl chloride.

After standing 20 hr at room temperature, the mixture was hydrolyzed by the addition of cold, dilute HCl. The precipitated oil was taken up in 40 ml of methylene chloride, washed once with cold, dilute HCl, once with water, once with cold sodium bicarbonate solution, once with water, dried over anhydrous Na_2SO_4, and the solvent removed by rotary evaporation to yield 2 g (76% yield) of an oil which solidified upon standing several hours. Two recrystallizations from petroleum ether (bp 30–60°)–ethyl acetate yielded the analytical sample, mp 44–45°.

Anal. Calcd for $C_{14}H_{15}F_3O_5S$: C, 47.72; H, 4.29; F, 16.18. Found: C, 47.96; H, 4.26; F, 16.11.

Cyclohexyl tosylate (**6**-H) was prepared in 75% yield by the previously published procedure,[3] mp 44.0–44.8° (lit.[18] mp 44.4–44.8°).

trans-**2-Methoxycyclohexanol** was prepared in 50% yield by the method described for *trans*-2-methoxycyclopentanol: bp 72–73° (10 mm); n^{25}D 1.4578 [lit.[19] bp 72.5–73.2° (10 mm); n^{25}D 1.4586]. Treatment of a portion of the alcohol with 3,5-dinitrobenzoyl chloride in pyridine yielded *trans*-2-methoxycyclohexyl 3,5-dinitrobenzoate, mp 101–101.5° (lit.[19] mp 101°).

trans-**2-Methoxycyclohexyl tosylate** (**6**-OME) was prepared in 62% yield by standard procedure.[3] The crude ester was purified three times by precipitation from petroleum ether (bp 30–60°) at Dry Ice–acetone temperature. The final traces of solvent were removed by flash distillation under reduced pressure (*ca.* 0.1 mm) to yield an oil of greater than 97% purity by infinity absorbance: ir (neat) 1335 (ν_{SO_2} asymmetric), 1163 (ν_{SO_2} symmetric), and 1090 cm^{-1} (ether COC).

trans-**2-Chlorocyclohexanol** was prepared in 80% yield by the method described for *trans*-2-chlorocyclopentanol, bp 70–71° (7 mm) [lit.[20] bp 71° (7 mm)]. Gc analysis indicated minimum purity of 99%.

trans-**2-Chlorocyclohexyl tosylate** (**6**-Cl) was prepared in 78% yield by standard procedure.[3] Four recrystallizations from petroleum ether (bp 30–60°)–benzene gave the analytical sample of the ester, mp 50–51°.

Anal. Calcd for $C_{13}H_{17}ClO_3S$: C, 54.07; H, 5.93; Cl, 12.28. Found: C, 53.82; H, 5.74; Cl, 12.49.

trans-**2-Trifluoroacetorycyclohexyl tosylate** (**6**-OTf) was prepared in 80% yield by the method described for **5**-OTf: mp 83–84° [after three recrystallizations from petroleum ether (bp 30–60°)–ethyl acetate].

Anal. Calcd for $C_{15}H_{17}F_3O_5S$: C, 49.17; H, 4.68; F, 15.56. Found: C, 49.22; H, 4.56; F, 15.80.

Registry No.—**5**-H, 3558-06-3; **5**-OTf, 19990-19-3; **5**-OMe, 19990-12-6; **5**-Cl, 19990-13-7; **6**-H, 953-91-3; **6**-OTf, 19990-15-9; **6**-OMe, 19990-16-0; **6**-Cl, 19990-17-1.

Acknowledgment.—Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society. The authors also gratefully acknowledge the valuable comments of Dr. Paul E. Peterson of Saint Louis University who assisted in both the direction and interpretation of the work.

(14) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N.Y., 1962, p. 229.
(15) W. Huckel and H. D. Sauerland, *Ann.*, **592**, 190 (1955).
(16) T. C. Briuee and T. H. Fife, *J. Amer. Chem. Soc.*, **84**, 1973 (1962).
(17) H. B. Donohue and C. A. Vanderwerf, *Org. Syn.*, **30**, 24 (1950).
(18) J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, **73**, 5034 (1951).
(19) S. Winstein and R. B. Henderson, *ibid.*, **65**, 2196 (1943).
(20) Alex Nikon, *ibid.*, **79**, 243 (1957).

Photochemical Reactions of Dimethyl Acetylenedicarboxylate with Benzene and Naphthalene[1]

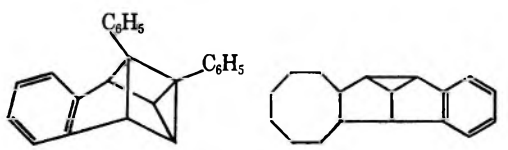
ERLING GROVENSTEIN, JR., THOMAS C. CAMPBELL, AND TOMOO SHIBATA

School of Chemistry of the Georgia Institute of Technology, Atlanta, Georigia 30332

Received November 14, 1968

The photochemical reaction of dimethyl acetylenedicarboxylate with benzene gives dimethyl cycloocta-1,3,5,7-tetraene-1,8-dicarboxylate. In contrast, photoreaction of dimethyl acetylenedicarboxylate with molten naphthalene gives dimethyl 1-naphthalenefumarate (VII), dimethyl 3,4-benzotricyclo[3.3.0.0.^{2,8}]octa-3,6-diene-6,7-dicarboxylate (IX), dimethyl 2-naphthalenefumarate (X), and dimethyl *trans*-acenaphthene-1,2-dicarboxylate (XI). Adduct XI has been shown to result from photocyclization of VII and also of dimethyl 1-naphthalenemaleate. In methanol as solvent photoadduct XI is the chief 1:1 adduct. The photochemical reaction in molten naphthalene (90°) is complicated by a thermal reaction of naphthalene with dimethyl acetylenedicarboxylate which gives dimethyl 1,4-dihydro-1,4-ethenonaphthalene-2,3-dicarboxylate (VI); the latter undergoes photolysis to give chiefly dimethyl benzocyclooctene-7,8-dicarboxylate (VIII) on short irradiation and isomeric products on long irradiation or irradiation in acetone as solvent.

While the photochemical reactions of benzene with maleic anhydride,[2] simple olefins,[3] conjugated dienes,[4] and acetylene derivatives[3c,5] have been studied in considerable detail and the mechanisms of these reactions are now partially understood,[6] corresponding reactions of naphthalene have been little investigated. No photochemical reaction of naphthalene with maleic anhydride has been found.[7] While β-methoxynaphthalene upon irradiation with ultraviolet (uv) light has been reported to give a dimer, similar products have not been obtained from naphthalene or other simple derivatives of naphthalene; moreover, β-methoxynaphthalene has been reported not to give photoadducts with maleic anhydride or dimethyl acetylenedicarboxylate.[8] Naphthalene has been reported to form readily 1:1 photoadducts with primary and secondary aliphatic amines; although the structures of these adducts have not been revealed, they are likely analogous to the corresponding 1,4 photoadducts of benzene.[9] While the present work was in progress,[10] naphthalene was reported[11] to undergo a photochemical addition of diphenylacetylene to give an adduct of structure I; similar products were obtained from dimethylnaphthalenes. More recently, in a brief statement, naphthalene was reported to form two 1:1 photoadducts with cyclooctene; spectroscopic evidence was said to be consistent with structure II for the major isomer.[3c] We wish to report some new types of photochemical adducts from reaction of naphthalene with dimethyl acetylenedicarboxylate and to report further details upon the reaction of benzene with dimethyl acetylenedicarboxylate.[5a,b]



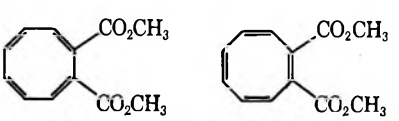
I

II

Results and Discussion

Benzene with Dimethyl Acetylenedicarboxylate.—The photochemical reaction of benzene with dimethyl acetylenedicarboxylate gives some 15% yield of dimethyl cyclooctatetraene-1,2-dicarboxylate together with unidentified products of higher molecular weight. The structure of the cyclooctatetraene derivative was deduced from physical and chemical properties which were given in a preliminary communication[5a] and were verified and extended by Bryce-Smith and Lodge.[5b] This structural assignment is now confirmed by comparisons of melting point, mixture melting point, and infrared (ir) spectrum with those of a sample of dimethyl cyclooctatetraene-1,2-dicarboxylate prepared by a copolymerization technique.[12]

In our preliminary communication[5a] we pointed out that the valence-bond structure of dimethyl cyclooctatetraene-1,2-dicarboxylate might be that of tautomer IIIa or IIIb. Shortly thereafter Anet[13] reported on the



IIIa IIIb

(1) Abstracted in large part from the Ph.D. thesis of T. C. Campbell, Georgia Institute of Technology, 1967.

(2) (a) H. F. Angus and D. Bryce-Smith, *J. Chem. Soc.*, 4791 (1960); (b) E. Grovenstein, Jr., D. V. Rao, and J. W. Taylor, *J. Amer. Chem. Soc.*, **83**, 1705 (1961); (c) G. O. Schenck and R. Steinmetz, *Tetrahedron Lett.*, 1 (1960).

(3) (a) R. Srinivasan and K. A. Hill, *J. Amer. Chem. Soc.*, **87**, 4653 (1965); (b) K. E. Wilzbach and L. Kaplan, *ibid.*, **88**, 2066 (1966); (c) D. Bryce-Smith, A. Gilbert, and B. H. Orger, *Chem. Comm.*, 512 (1966); (d) N. C. Perrins and J. P. Simmons, *ibid.*, 999 (1967).

(4) G. Koltzenburg and K. Kraft, *Tetrahedron Lett.*, 389 (1966).

(5) (a) E. Grovenstein, Jr., and D. V. Rao, *ibid.*, 148 (1961); (b) D. Bryce-Smith and J. E. Lodge, *J. Chem. Soc.*, 695 (1963); (c) J. G. Atkinson, D. E. Ayer, G. Büchi, and E. W. Rabb, *J. Amer. Chem. Soc.*, **85**, 2257 (1963).

(6) D. Bryce-Smith and H. C. Longuet-Higgins, *Chem. Comm.*, 593 (1966), and references cited therein.

(7) G. O. Schenck, J. Kuhls, S. Mannsfeld, and C. H. Krauch, *Chem. Ber.*, **96**, 813 (1963).

(8) J. S. Bradshaw and J. S. Hammond, *J. Amer. Chem. Soc.*, **85**, 3953 (1963).

(9) M. Bellas, D. Bryce-Smith, and A. Gilbert, *Chem. Comm.*, 862 (1967).

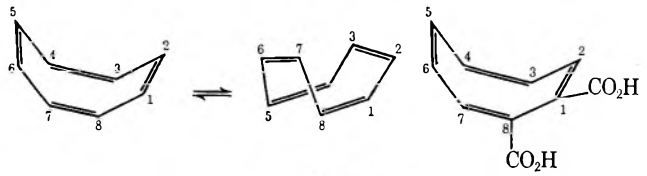
(10) We wish to thank Messrs. W. E. McGonigal, P. G. Arapakos, F. W. Walker, and G. Cohn for conducting many of the difficult preliminary phases of this investigation.

(11) W. H. F. Sasse, P. J. Collin, and G. Sugowdz, *Tetrahedron Lett.*, 3373 (1965); P. J. Collin and W. H. F. Sasse, *ibid.*, 1689 (1968).

(12) This sample was kindly supplied by the late Dr. Arthur C. Cope and was prepared by a copolymerization technique given in the Ph.D. thesis of J. E. Meili, Massachusetts Institute of Technology, 1952 [*cf.* A. C. Cope and H. C. Campbell, *J. Amer. Chem. Soc.*, **73**, 3536 (1951); **74**, 179 (1952); A. C. Cope and D. S. Smith, *ibid.*, **74**, 5136 (1952)]. Reduction of this dimethyl ester with lithium aluminum hydride gave a glycol which was identical with the glycol prepared from 2-butyne-1,4-diol diacetate by a copolymerization procedure; finally all of the isomeric cyclooctatetraenedicarboxylic acids have been prepared by oxidation of the corresponding diacetyl cyclooctatetraenes (personal communication from the late Dr. A. C. Cope).

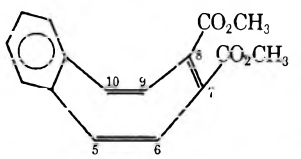
(13) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 671 (1962).

basis of an nmr study that there is a rapid equilibrium between the two identical, nonplanar tautomers (IVa and IVb) of cyclooctatetraene with the life time of a



IVa IVb V

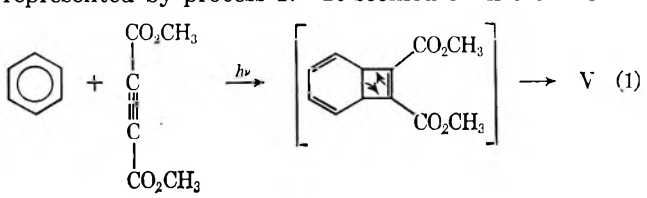
tautomer being only about 0.04 sec at −10°. Bryce-Smith and Lodge[5b] have noted that the failure of the dicarboxylic acid derived from dimethyl cyclooctatetraene-1,2-dicarboxylate to give an anhydride under conventional means is consistant with tautomeric structure V for the dicarboxylic acid since in this structure the carboxyl groups are oriented away from one another at a skew angle of about 70°.[14] The nmr spectrum of dimethyl cyclooctatetraene-1,2-dicarboxylate in chloroform solution (see Experimental Section) has the doublet assigned to the protons adjacent to the carboxylate groups split by only 1.9 Hz; this small coupling constant is in agreement with a structure analogous to V for the dimethyl ester since the protons on C-2 and C-7 are at a skew angle of about 70° to the adjacent protons on C-3 and C-6.[15] Some confirmation of this structure is provided by the nmr spectrum of dimethyl benzocyclooctene-7,8-dicarboxylate (see later discussion) which must, on general considerations, exist almost entirely in the tautomeric form VIII and whose



VIII

corresponding acid is readily converted into an anhydride. For this compound the coupling constant between protons on C-5 and C-6 (C-9 and C-10) is 11 Hz as expected for *cis* protons on an olefinic double bond.[15] The reason why tautomeric structure V is more stable than the alternative structure (in absence of other factors which exist for VIII) appears to be that this structure minimizes repulsions between the carboxyl groups (*cf.* the greater stability of fumaric over maleic acid); also in structure V two double bonds are conjugated, one to each carboxyl group, whereas in the alternative structure only one double bond is effectively conjugated to both carboxyl groups.

In summary the photochemical reaction between benzene and dimethyl acetylenedicarboxylate can be represented by process 1. It seemed of interest to see



V (1)

(14) A similar conclusion was relayed to us in a personal communication in 1961 by the late Dr. A. C. Cope who also reported unsuccessful attempts to resolve the dicarboxylic acid with two optically active bases and noted "failure to resolve the acid if it has that structure (V) can be explained by spontaneous racemization through a planar structure, but of course an unsuccessful resolution is not definitive."

if naphthalene can undergo a similar reaction with dimethyl acetylenedicarboxylate.

Naphthalene with Dimethyl Acetylenedicarboxylate.—Irradiation of a solution of dimethyl acetylenedicarboxylate in a 14-fold molar excess of molten naphthalene at 90° with uv light for 4 days in a quartz apparatus gave a complex mixture of products from which unreacted naphthalene was separated by distillation *in vacuo* at 100° and less soluble materials were removed by solvent precipitation from petroleum ether. The soluble product according to vapor phase chromatography (vpc) contained about an 11% yield of 1:1 adducts. These are designated, in order of increasing retention times, as VI–XI and were formed in relative proportions of 3, 34, 6, 34, 10, and 13%, respectively. The more abundant products, VII and IX, were separated by chromatography on silica gel and were purified by recrystallization. Irradiation of a solution of dimethyl acetylenedicarboxylate and a twofold molar excess of naphthalene in methanol at reflux temperature for 60 hr gave some 10% yield[16] of 1:1 photoadducts VII, IX, X, and XI in relative amounts of 8, 7, 9, and 76%, respectively. Following an isolation procedure like that for VII and IX, adduct XI was obtained in 7% over-all yield after recrystallization from methanol.

Adduct VI, which was not formed in appreciable quantity in the photochemical reaction at lower temperature, was found to be identical in vpc retention time on two columns (Apiezon L and silicone gum rubber) with the 1:1 adduct formed by thermal reaction of dimethyl acetylenedicarboxylate with excess naphthalene (25% yield of crystalline adduct after 3 days at 170–180° or 2.9% yield after 7 days at steam-bath temperature). According to its mode of formation,[17] analysis, molecular weight, and spectral properties, this previously unknown adduct, mp 76.5–77.0°, should have the structure of dimethyl 2,3-benzobicyclo-[2.2.2]octatriene-5,6-dicarboxylate (dimethyl 1,4-dihydro-1,4-ethenonaphthalene-2,3-dicarboxylate) expected for a normal Diels–Alder addition. This structure was confirmed by hydrogenation in ethyl acetate over a palladium catalyst which proceeded with absorption of 2 molar equiv of hydrogen to give a product of mp 90.5–91.0°, with melting point and nmr spectrum identical with the reported values for *exo*-dimethyl 2,3-benzobicyclo[2.2.2]octa-2-ene-5,6-dicarboxylate.[18]

Irradiation of dimethyl 2,3-benzobicyclo[2.2.2]octatriene-5,6-dicarboxylate in methanol solution with uv light through a Pyrex filter gave an 80% yield of a white crystalline product, mp 77.0–77.5°, which was identical in vpc retention time on two columns with the adduct VIII above. This compound has an analysis and a molecular weight corresponding to $C_{16}H_{14}O_4$.

(15) *Cf.* J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J. 1965, pp 114–18.

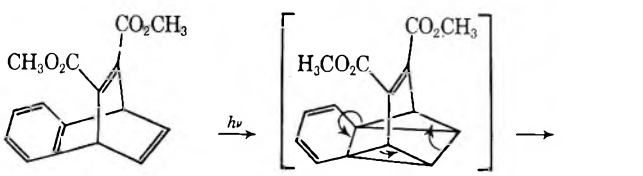
(16) The reaction in methanol is complicated by photochemical addition of methanol to dimethyl acetylenedicarboxylate. *Cf.* the photochemical addition of 2-propanol to acetylenedicarboxylic acid [G. O. Schenck and R. Steinmetz, *Naturwissenschaften*, **47**, 514 (1960); M. Pfau, R. Dulou, and M. Vilkas, *Compt. Rend.*, **251**, 2188 (1960)].

(17) (a) *Cf.* the thermal addition of dicyanoacetylene to naphthalene[17b] and to 1,4-diphenylnaphthalene[17c] and of benzyne to naphthalene.[17d] (b) R. C. Cookson and J. Dance, *Tetrahedron Lett.*, 879 (1962); (c) C. Dufraisse, J. Rigaudy, and M. Ricard, *Tetrahedron*, 491 (1966); (d) R. G. Miller, and M. Stiles, *J. Amer. Chem. Soc.*, **85**, 1798 (1963).

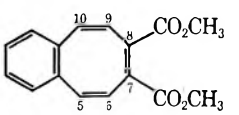
(18) K. Takeda, K. Kitahonoki, M. Sugiura, and Y. Takano, *Chem. Ber.*, **95**, 2344 (1962); K. Tori, Y. Takano, and K. Kitahonoki, *ibid.*, **97**, 2798 (1964).

The nmr spectrum (in CCl_4) shows four aromatic protons centered at τ 2.9 (symmetrical multiplet), two vinyl protons in a doublet at 3.29 (J = 11.3 Hz), two more vinyl protons in a doublet at 3.89 (J = 11.3 Hz), and six methoxyl protons in a singlet at 6.35. The coupling constant between the vinyl protons is consistent[15] with the protons on the double bond being *cis*. The methoxyl singlet indicates that the carbomethoxyl groups are equivalent and together with the simplicity of the remainder of the spectrum gives evidence that the molecule has a plane of symmetry. The uv absorption [$\lambda_{max}^{C_2H_5OH}$ 200 mμ (ϵ 30,500), shoulders at 230 (20,500) and 290 (1800)] is similar to that of benzocyclooctatetraene[19] and dimethyl cyclooctatetraene-1,2-dicarboxylate.[5a,b] In agreement with expectations for a benzocyclooctatetraene derivative, hydrogenation over a palladium catalyst in ethyl acetate solution gave an uptake of 3 molar equiv of hydrogen. Finally saponification of the ester and vacuum sublimation of the resulting carboxylic acid at 180° gave a yellow cyclic anhydride, $C_{14}H_8O_3$; this result demonstrates that the carboxyl groups of VIII are on adjacent carbon atoms. The sum of the available evidence requires that compound VIII have the structure of dimethyl benzocyclooctene-7,8-dicarboxylate.

The photolysis of dimethyl 2,3-benzobicyclo[2.2.2]-octatriene-5,6-dicarboxylate to give dimethyl benzocyclooctene-7,8-dicarboxylate can be rationalized by process 2 which proceeds by the vinyl–benzo cyclo-

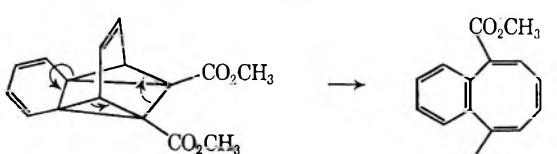


VI XII



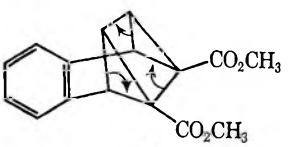
VIII (2)

adduct XII analogous to that recently reported[20] for 2,3-benzobicyclo[2.2.2]octatriene ("benzobarrelene") itself. A second vinyl–benzo cycloadduct XIII could also be visualized in the present case; however, this should give dimethyl benzocyclooctene-5,10-dicarboxylate (XIV). Also the vinyl–vinyl cycloadduct XV

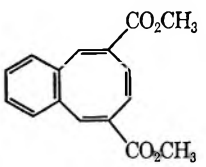


XIII XIV

could be formed and this should give appreciable amounts of both dimethyl benzocyclooctene-7,8-dicarboxylate (VIII) and 6,9-dicarboxylate XVI. No evidence for the formation of XIV and XVI has been found; however, prolonged irradiation of VI resulted in disappearance of initially formed VIII and appearance



XV



(and VIII)

XVI

of unidentified products, chiefly a product of slightly longer retention time than photoadduct IX. The formation of VIII as the initial major product of photolysis confirms the elegant deuterium tracer studies of Zimmerman and coworkers[20] which demonstrated that vinyl–benzo cycloaddition is preferred over vinyl–vinyl cycloaddition in the direct photolysis of "benzobarrelene." The present work also demonstrates that intermediate XII is preferred over XIII. The direct photolysis likely involves singlet excitation of VI. If the photolysis is run in acetone solution (Pyrex filter), three isomeric products result, of which one is likely dimethyl 3,4-benzotricyclo[3.3.0.0^{2,8}]octa-3,6-diene-5,6-dicarboxylate (IX) (see later discussion). These products evidently result from a triplet excited state *via* acetone sensitization; analogous results have been obtained in the simpler case of "benzobarrelene."[20]

The pale yellow photoadduct VII, mp 62.0–63.0°, which is a major product from the photochemical reaction of dimethyl acetylenedicarboxylate with molten naphthalene, is assigned the structure of dimethyl 1-naphthalenefumarate. This compound has the correct elemental analysis and molecular weight for a 1:1 adduct, $C_{16}H_{14}O_4$, and has uv absorption somewhat similar to that of a 1-vinylnaphthalene.[21a] The nmr spectrum showed two nonequivalent methoxyl singlets and eight protons in the region τ 2.2–3.0. That the vinyl proton of VII absorbs in the normal aromatic region is to be expected since the vinyl protons of diethyl fumarate absorb at τ 3.17.[21b] Hydrogenation of VII resulted in uptake of 1 molar equiv of hydrogen and gave a colorless compound of mp 60.0–60.5°. This compound was found to be identical with a synthetic sample of dimethyl 1-naphthalenesuccinate prepared from the known compound 1-naphthalenemaleic anhydride[22] by esterification and hydrogenation. Since the dimethyl ester of 1-naphthalenemaleic anhydride is an oil of different vpc retention time from that of VII, the crystalline photoadduct VII is evidently the *trans* isomer, dimethyl 1-naphthalenefumarate.

The colorless photoadduct IX, mp 86.5–87.0°, is another of the major products from the photochemical reaction of dimethyl acetylenedicarboxylate with molten naphthalene. This compound has the correct

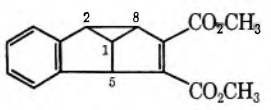
(19) G. Wittig, H. Eggers, and P. Duffner, *Ann. Chem.*, **619**, 10 (1958).

(20) H. E. Zimmerman, R. S. Givens, and R. M. Pagni, *J. Amer. Chem. Soc.*, **90**, 4191 (1968); *cf.* G. R. Ziegler and G. S. Hammond, *ibid.*, **90**, 513 (1968); P. W. Rabideau, J. B. Hamilton, and L. B. Friedman, *ibid.*, **90**, 4465 (1968); J. P. N. Brewer and H. Heaney, *Chem. Comm.*, 811 (1967).

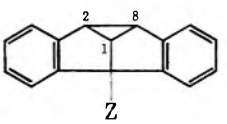
(21) (a) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1951, spectra no. 232 and 233. (b) N. S. Bhacca, L. F. Johnson and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, spectrum no. 213.

(22) L. Denivelle and D. Razavi, *Compt. Rend.*, **237**, 570 (1953).

elementary analysis and molecular weight for a 1:1 adduct, $C_{16}H_{14}O_4$, and has the following spectral properties: λ_{max}^{EtOH} 200 mμ (ε 42,500), 220 (shoulder, 19,650), 265 (4770); nmr ($CDCl_3$) at τ 2.4–3.1 (4 H, complex multiplet), 5.81 (1 H, doublet, J = 5.9 Hz), 6.37 (3 H, singlet), 6.42 (3 H, singlet), 6.5–6.9 (2 H, complex multiplet), 6.9–7.3 (1 H, complex multiplet). Hydrogenation with a palladium catalyst in acetic acid resulted in uptake of 2 molar equiv of hydrogen. No deuterium exchange was observed after refluxing in 3.5 *M* $NaOCH_3$ in CH_3OD for 48 hr. Oxidation by $KMnO_4$ in aqueous acetone containing a little acetic acid and esterification of the acidic products with diazomethane gave 55% yield of dimethyl phthalate. It is believed that these data are best explained on the basis of the structure dimethyl 3,4-benzotricyclo[3.3.0.$0^{2,8}$]octa-3,6-diene-6,7-dicarboxylate for adduct IX. This structure accounts for the four aromatic protons in the nmr spectrum and the oxidation to phthalic acid. The

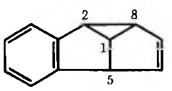


IX



Z

XVII, Z = H
XVIII, Z = CO_2CH_3

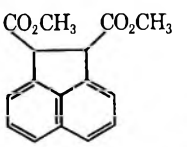


XIX

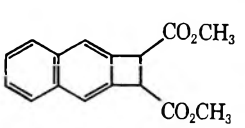
nonaromatic portion of the nmr spectrum of IX may be interpreted as follows: the six protons, three each at τ 6.37 and 6.42, correspond to two carbomethoxyl groups which are in nonequivalent locations as given in the proposed structure; the single proton (doublet) at τ 5.81 corresponds to the proton on C-5 (*cf.* the proton on C-5 in XVII which absorbs as a doublet at 5.68[23] and the corresponding proton in XIX which absorbs at 6.1–6.3 with J_{15} = 6.0 Hz[20]); the proton at τ 6.9–7.3 corresponds to that on C-2 (*cf.* the proton on C-2 in XVII which absorbs at 7.10,[23] that in XVIII at 6.92,[24] and that in XIX at 7.0–7.3[20]); the two protons at τ 6.5–6.9 correspond to those on C-1 and C-8 (*cf.* the proton on C-1 in XVII which absorbs at 6.47,[23] and the protons on C-1 and C-8 of XIX which absorb at 6.7–7.0 and 7.3–7.6, respectively[20]). Hydrogenation of IX resulted in absorption of 2 molar equiv of hydrogen, corresponding to reduction of the double bond and the cyclopropane ring. Reduction of the double bond first followed by reduction of the cyclopropane ring would lead to at least two compounds since two bonds of the cyclopropane ring of IX are benzylic and nearly equally likely to be reduced; in fact, hydrogenation of IX afforded two products according to vpc analysis.

Photoadduct X, which was not isolated in a pure state, was found to be identical in vpc retention time on two columns with a sample of dimethyl 2-naphthalenefumarate, mp 51.8–52.5°, prepared from the known compound 2-naphthalenemaleic anhydride[22] by esterification and photoisomerization. The structure of dimethyl 2-naphthalenefumarate was confirmed both by its spectral properties and by hydrogenation to dimethyl 2-naphthalenesuccinate.

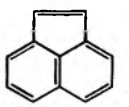
The photoadduct XI, mp 84.5–85.0°, is the major 1:1 adduct from photochemical reaction of dimethyl acetylenedicarboxylate with naphthalene in hot methanol and is also formed from the same reaction in molten naphthalene. This colorless adduct, of analysis and molecular weight corresponding to $C_{16}H_{14}O_4$, has uv absorption similar to that of acenaphthene.[25] The nmr spectrum shows six aromatic protons at τ 2.3–2.9, two benzyl protons in a singlet at 4.95, and six methoxyl protons in a singlet at 6.33. The two benzylic protons are readily exchanged for deuterium using sodium methoxide in CH_3OD. This ready exchange implies that both protons are on carbon atoms adjacent to carbomethoxyl groups. Adduct XI failed to absorb any hydrogen over a palladium-on-charcoal catalyst under general conditions which were successful with the other adducts reported here. On the basis of the evidence presented so far, XI might have either structure XX or XXI. A distinction between these possibil-



XX



XXI



XXII

ities was obtained by the following degradation. Saponification of the adduct with alcoholic KOH gave the corresponding dicarboxylic acid (as shown by reaction with diazomethane to regenerate XI). Oxidation of this acid with lead tetraacetate[2b] in pyridine for 5 min at 70° gave acenaphthylene XXII which was identified by comparison with an authentic sample; hence adduct XI must have the structure XX. The more stable *trans* structure is assigned to XI in view of failure to detect any appreciable isomerism of XI with sodium methoxide under conditions which exchanged the hydrogen atoms α to the carbomethoxy groups, failure to obtain a volatile anhydride upon refluxing the acid with acetic anhydride, and failure of the corresponding di-N-benzylamide to give a cyclic imide in trifluoroacetic acid under conditions wherein the di-N-benzylamide of naphthalene-2,3-dicarboxylic acid gave an imide in good yield. In conclusion adduct XI is assigned the structure of dimethyl *trans*-acenaphthene-1,2-dicarboxylate.[26]

While photoadducts IX, X, and XI appear to be stable under the usual conditions of irradiation, dimethyl 1-naphthalenefumarate (VII) in methanol solution upon irradiation through a Pyrex filter gave a 59% yield of dimethyl *trans*-acenaphthene-1,2-dicarboxylate (XI). Irradiation of dimethyl 1-naphthalenemaleate under similar conditions gave as high as 92.5% yield of XI; in the early stages of the photolysis much of the dimethyl 1-naphthalenemaleate was transformed to dimethyl 1-naphthalenefumarate before cyclization to XI.

(23) G. F. Emerson, L. Watts, and R. Pettit, *J. Amer. Chem. Soc.*, **87**, 131 (1965).

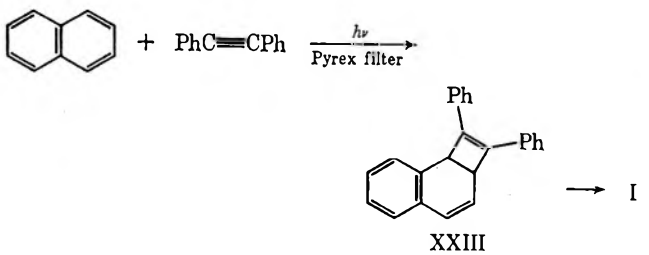
(24) E. Ciganek, *ibid.*, **88**, 2882 (1966).

(25) See ref 21a, spectrum no. 212.

(26) We are indebted to Dr. Charles L. Liotta for first suggesting to us this possible structure.

Conclusions

Whereas the photochemical reaction of benzene with dimethyl acetylenedicarboxylate proceeds by 1,2–1,2 addition[5a,b] to give finally dimethyl cycloocta-1,3,5,7-tetraene-1,8-dicarboxylate, the corresponding reaction of naphthalene follows a diverse course. This is surprising since the photochemical reaction[11] of naphthalene with diphenylacetylene follows a path analogous to that of benzene except that the intermediate XXIII

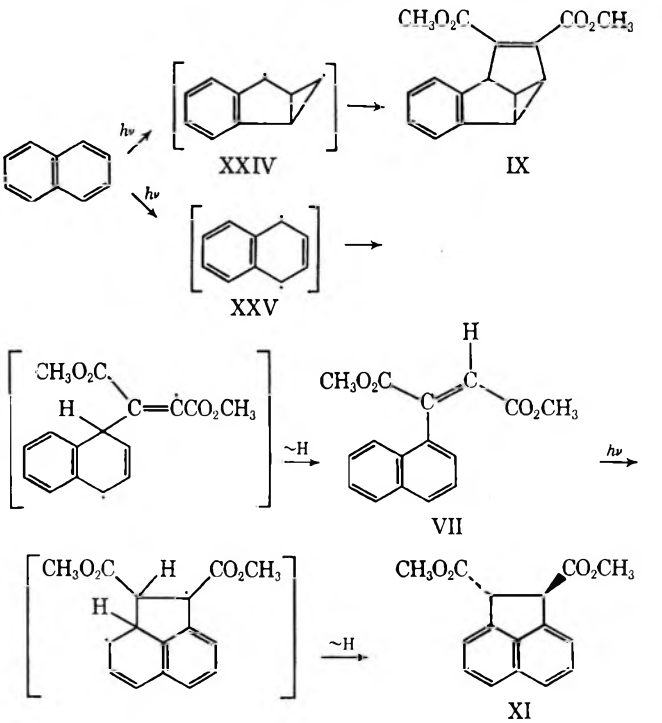


XXIII

undergoes an intramolecular 1,2–1,2 addition to give I rather than tautomerism to a benzocyclooctatetraene. A reasonable explanation begins with the postulate that the photochemical reaction of naphthalene with diphenylacetylene (with use of Pyrex filter[11]) involves photochemical activation of diphenylacetylene rather than naphthalene in accord with likely activation[6] of dimethyl acetylenedicarboxylate rather than benzene in the reaction leading to dimethyl cycloocta-1,3,5,7-tetraene-1,8-dicarboxylate. This postulate appears reasonable since diphenylacetylene has a strong absorption maximum at 298 mμ (ε 25,000) while naphthalene has comparatively weak absorption in this area [298 mμ (ε 320)].[27] The photoreaction of molten naphthalene with dimethyl acetylenedicarboxylate gives about the same mixture of 1:1 adducts (though in reduced yield) with use of a Pyrex filter as without a filter. Since dimethyl acetylenedicarboxylate has only negligible absorption[5b] at wavelengths longer than 300 mμ, while naphthalene has weak but appreciable absorption [at 300 mμ (ε 280), 311 (250)] and was in large excess, we believe that the present photochemical reactions are initiated by photoexcitation of naphthalene which then combines with the acetylenic ester.

The photoadducts VII, IX, and XI are conveniently rationalized by the scheme shown (see Scheme I). Intermediates XXIV and XXV could be in singlet and triplet states, respectively, in analogy with suggestions for the corresponding biradicals from photoexcitation of benzene;[6] however, at present, we think that the question of the multiplicity of these intermediates should be left open. Dimethyl 2-naphthalenefumarate X is likely formed by a path analogous to that for VII. The formation of IX is similar to the photoreaction of naphthalene with cyclooctene to give II.[3c] The formation of dimethyl 1- and 2-naphthalenefumarates in fair yield (8.3% VII and of its photoproduct XI and 0.9% X in methanol) appears to be without good precedent,[28] although trace amounts (<0.5%) of cyclooctylbenzene

SCHEME I



are reported in the photoreaction of benzene with cyclooctene.[3c]

The photocyclization of dimethyl 1-naphthalenefumarate (VII) and dimethyl 1-naphthalenemaleate to give good yields of dimethyl *trans*-acenaphthene-1,2-dicarboxylate also seems to be without good precedent for a homocyclic system. The photocyclization of *trans*-1,3-diphenylpropene to 1-phenylindan (5% yield) appears at first hand to be a similar process; however, this reaction was interpreted as a 1,2 migration of either phenyl or hydrogen to give a 1,3 diradical XXVI or XXVII which then underwent cyclization followed by

PhĊHCH$_2$ĊHPh — XXVI

PhĊHCHPhĊH$_2$ — XXVII

rearomatization to give 1-phenylindan or cyclization in an alternative way to give *cis*- and *trans*-1,2-diphenylcyclopropanes (each in 6% yield).[29] A more analogous cyclization, but to a heterocyclic system, is the photocyclization of alkyl-substituted arylic acid anilides to dihydrocarbostyrils,[30] which has been suggested to proceed by a mechanism like that for the conversion of VII into XI in Scheme I.

Adducts VI and VIII are *not* formed in appreciable amount under the present conditions by photochemical reaction of naphthalene with dimethyl acetylenedicarboxylate, but instead dimethyl 1,4-dihydro-1,4-ethenonaphthalene-2,3-dicarboxylate (VI) is formed by a thermal reaction of naphthalene with dimethyl acetylenedicarboxylate at 90° as confirmed by a test experiment in absence of light. Moreover, when the photochemical reaction is run at room temperature in benzene, methanol, or cyclohexane as solvent, no appreciable quantity of VI or VIII is detectable. Finally

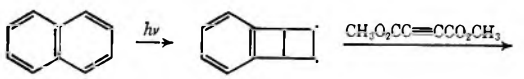
(27) See ref 21a, spectra no. 131 and 195; however, for a recent contrary conclusion, see R. J. McDonald and B. K. Selinger, *Tetrahedron Lett.*, 4791 (1968).

(28) Recently the photochemical reaction of naphthalene with acrylonitrile has been reported to give 8-cyano-2,3-benzobicyclo[4.2.0]octa-2,4-diene (*cf.* XXIII) and substituted naphthalenes, evidently 2-(1-naphthyl)- and 2-(2-naphthyl)propionitrile [J. J. McCullough, C. Calvo, and C. W. Huang, *Chem. Comm.*, 1176 (1968)].

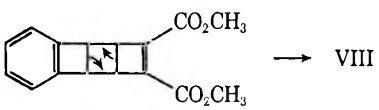
(29) G. W. Griffin J. Covell, R. C. Petterson, R. M. Dodson, and G. Klose, *J. Amer. Chem. Soc.*, **87**, 1410 (1965); G. W. Griffin, A. F. Marcantonio, H. Kristinsson, R. C. Petterson and C. S. Irving, *Tetrahedron Lett.*, 2951 (1965); *cf.* H. Kristinsson and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 5968 (1967).

(30) P. G. Cleveland and O. L. Chapman, *Chem. Comm.*, 1964 (1967).

dimethyl benzocyclooctene-7,8-dicarboxylate (VIII) results from photochemical isomerism of VI. These conclusions are of interest since concerted 1,4 addition of dimethyl acetylenedicarboxylate to naphthalene is not allowed according to orbital symmetry rules[31] as a photochemical reaction but is allowed as a thermal reaction (Diels–Alder reaction). The path shown below, which at first hand might appear attractive by



XXVIII



analogy with similar additions of olefins to benzene[6] is evidently not a favored path for naphthalene. A likely reason is that the presumed intermediate XXVIII is destabilized by steric strain resulting from fusion of the benzene ring to the bicyclic biradical; this additional strain is, of course, absent in the case of photolysis of benzene itself. The greater rigidity of the naphthalene nucleus may also be a factor in explaining why 1,2-dimethylnaphthalene does not isomerize to 1,3-dimethylnaphthalene upon irradiation (mercury lamp, quartz apparatus)[32] while photorearrangements of alkyl groups upon the benzene nucleus are now well known, *e.g.*, *o*-xylene to *m*-xylene.[33]

Finally, the variation of product composition with solvent in the photoreaction of naphthalene with dimethyl acetylenedicarboxylate is worthy of comment. In molten naphthalene as solvent the ratio of adducts (VII plus XI)/IX is 1.4 and drops to about half this value in cold benzene; however, in cold or hot methanol this ratio is about 12 and is only slightly less in cold cyclohexane. The relative yield of X/IX follows a similar trend with solvent composition. The explanation of these apparent solvent effects must await a more detailed study of reaction mechanism, but practical advantage was afforded by these large variations in facilitating isolation of products in the present work.

Experimental Section[34]

Photochemical reactions were run in a cylindrical quartz cell which had an inner jacket for water cooling (or heating) and an outer jacket of 350-ml capacity for the reaction mixture. Nitrogen could be bubbled through the reaction solution and a Pyrex filter could be inserted between the lamp and the cell to eliminate nearly all irradiation below 3000 Å if desired. Radiant energy was supplied by a medium-pressure mercury lamp (type LL) of 30-cm arc length made by the Hanovia Chemical and Manufacturing Co., Newark, N. J.; this lamp operated on about 1000 W at a current of 3.8 to 4.2 A.

Irradiation of Dimethyl Acetylenedicarboxylate in Benzene.—Dimethyl acetylenedicarboxylate (20 ml) dissolved in 300 ml of thiophene-free benzene was placed in the water-cooled quartz cell and irradiated for 24 hr. The benzene and unreacted dimethyl acetylenedicarboxylate (some 14 g recoverable) were removed *in vacuo* on a rotating evaporator with heat supplied as required by a steam bath. The residue was distilled in a modified Hickman still[35] at 50 μ and a bath temperature of 90–150° and gave, after washing with a little alcohol, 0.7–0.8 g of crude yellow crystals. A dark red glassy residue remained undistilled; this residue is soluble in benzene and in acetone but has not been further investigated. The crude yellow crystals were combined with crystals from a similar run and upon sublimation at 102° (30 μ) gave 1.4 g of crystals of mp 107.2–108.6°. After two recrystallizations from methanol and resublimation, 0.8 g of pale yellow crystals of mp 109.4–110.4° was obtained. On the basis of previously reported physical and chemical properties[5a,b] this compound was assigned the structure of dimethyl cyclooctatetraene-1,2-carboxylate. This structure is supported by the nmr absorption ($CDCl_3$) at τ 2.84 (2 H, doublet, J = 1.9 Hz), 4.02 (4 H, unsymmetrical multiplet), and 6.30 (6 H, singlet) which are assigned, respectively, to ring protons adjacent to carbomethoxyl groups, other ring protons, and methoxyl protons. A sample of dimethyl cyclooctatetraene-1,2-dicarboxylate[12] kindly supplied by the late Dr. Arthur C. Cope had mp 109.0–110.9°, gave no mixture melting point depression, and had an ir spectrum (KBr disk) identical with that of the photochemical adduct.

Similar photochemical preparations of dimethyl cyclooctatetraene-1,2-dicarboxylate from 5.0 ml of dimethyl acetylenedicarboxylate rather than 20 ml gave 0.5–0.7 g of isolable crude crystalline product after 26 hr or irradiation; increasing the irradiation time to 96 hr gave 0.8 g of product. Photolysis of 5.0 ml of dimethyl acetylenedicarboxylate in 325 ml of benzene for 20 hr under a nitrogen atmosphere gave, according to product analysis by vpc on the silicon gum rubber column, 1.33 g (15% yield) of dimethyl cyclooctatetraene-1,2-dicarboxylate. The present photolyses are accompanied by the formation of a yellow-orange film on the inner wall of the quartz cell next to the light source. This film is derived at least in part from the acetylenic ester since it can be removed from the cell wall by treatment with alcoholic KOH (no appreciable solution but immediate dark red coloration of the film) followed by solution in water.

When dimethyl cyclooctatetraene-1,2-dicarboxylate (1.5 g) dissolved in a minimum quantity of absolute ethanol was treated with 2 g of potassium hydroxide dissolved in 20 ml of hot ethanol, there was an immediate dark red coloration which nearly disappeared within 1 min as tan-yellow crystals of the potassium salt of cyclooctatetraene-1,2-dicarboxylic acid appeared. These crystals after some 15 min were separated by filtration, washed with a little absolute ethanol, and acidified with hydrochloric acid to yield cyclooctatetraene-1,2-dicarboxylic acid. This acid after two recrystallizations from water gave canary yellow crystals, mp 206–208° dec, of satisfactory analysis[5a] for $C_{10}H_8O_4$. This acid (0.1 g) could be sublimed at 40 μ at a bath temperature of 180–200° without detectable decomposition into the corresponding anhydride (melting point, analysis, and ir spectral comparison); however, when the acid was heated in a sublimation apparatus at a bath temperature of 235–240° (20 mm), the sublimate which is obtained is of ill-defined melting point and, in large part, will not resublime 200° (5 μ).

Irradiation of Dimethyl Acetylenedicarboxylate with Naphthalene. A. In Molten Naphthalene.—A solution of 307 g (2.40 mol) of molten naphthalene (Baker reagent grade) and 20 ml (0.160 mol) of dimethyl acetylenedicarboxylate (redistilled *in vacuo*) was placed in the quartz cell and kept at 90 ± 3° by passing hot water through the inner compartment during irradiation for 4 days. The unreacted starting materials were removed from the deep red solution with the aid of a rotating evaporator, equipped with a Dry Ice condenser, at a final pressure of 0.1 mm on a steam bath. The nonvolatile residue weighed 20 g. This was dissolved in 50 ml of chloroform and the solution was poured slowly into 3 l. of 30–60° petroleum ether. A

(31) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

(32) Unpublished experiments with T. Shibata.

(33) R. B. Cundall and A. J. R. Voss, *Chem. Comm.*, 902 (1968); H. R. Ward, *J. Amer. Chem. Soc.*, **89**, 2367 (1967).

(34) Melting points were determined on a Mel-Temp apparatus and are corrected. Proton magnetic resonance (pmr) spectra were obtained at 60 MHz on a Varian A-60A spectrometer relative to tetramethylsilane as an internal standard. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer. Infrared spectra were measured on a Perkin-Elmer Model 237 Infracrod. Vapor phase chromatographs were obtained on an F & M Scientific Co. Model 810 research chromatograph equipped with dual flame ionization and thermal conductivity detectors with use of either 12 ft × 0.25 in. stainless steel columns packed with 10% SE-30 silicone gum rubber on 80–100 mesh Diatoport S (acid washed, treated with dimethyldichlorosilane) or 5 ft × 0.25 in. stainless steel columns packed with 10% Apiezon L on 60–80 mesh Chromosorb P (acid washed, silanized with dimethyldichlorosilane). Elemental analyses and molecular weight determinations were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(35) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 66.

flocculent precipitate formed immediately; this (7 g) was removed by filtration and discarded. The solvent was removed from the filtrate *in vacuo*. Analysis of the petroleum ether soluble residue (12.9 g) on the Apiezon L column at 260° gave dimethyl 1,4-dihydro-1,4-ethenonaphthalene-2,3-dicarboxylate (VI, 6.2 min, 0.13 g, 0.30%), dimethyl 1-naphthalenefumarate (VII, 7.0 min, 1.6 g, 3.6%), dimethyl benzocyclooctene-7,8-dicarboxylate (VIII, 7.5 min, 0.28 g, 0.64%), dimethyl 3,4-benzotricyclo[3.3.0.$0^{2,8}$]octa-3,6-diene-6,7-dicarboxylate (IX, 8.5 min, 1.6 g, 3.6%), dimethyl 2-naphthalenefumarate (X, 9.5 min, 0.50 g, 1.2%), and dimethyl *trans*-acenaphthene-1,2-dicarboxylate (XI, 10.5 min, 0.59 g, 1.4%). The indicated per cent yields are based upon the starting quantity of dimethyl acetylenedicarboxylate in the reaction mixture. A similar photochemical reaction but with an irradiation time of only 24 hr gave 4.5 g of petroleum ether soluble product, and another run with an irradiation time of 6 hr gave 1.6 g of such product. The combined crude product (19 g) from these three runs was chromatographed on a column (5.5 × 108 cm) packed with 1140 g of Brinkman Instruments Co. No. 7734 silica gel wet with petroleum ether. Elution with 4 l. of benzene gave 2.4 g of naphthalene and unknown substances; elution with 2 l. of 3% (by volume) ethyl ether in benzene gave 0.3 g of unknown; elution with 3 l. of 5% ethyl ether in benzene gave 7.4 g of 1:1 photoadducts; and prolonged elution (finally with 50:50 benzene–acetone) gave 8.3 g of unknown products. The middle fraction (6.5 g) of the 1:1 photoadducts was rechromatographed on silica gel wet with petroleum ether (column 4.1 × 85 cm). Elution with 1% ethyl ether in benzene gave 0.03 g of unknown after 3 l. of eluent and then 1.2 g (fraction A) in the next 0.5 l. of eluent; continued elution with 0.5 l. of the same solvent and then 1.2 l. of 5% ethyl ether in benzene gave 2.2 g of complex mixtures of adducts; and final elution with 0.5 l. of 5% acetone in benzene gave 2.6 g (fraction B). Fraction A according to vpc analysis consisted of eight parts VII, one part X, and two and one-half parts XI. Fraction A dissolved in 5 ml of methanol, was cooled to −78° to initiate crystallization and stored in a freezer for 2 days. After separation by filtration 0.17 g of cream-colored crystals, mp 61–63°, were obtained; these were about 95% pure VII according to vpc analysis and, after two recrystallizations from methanol, consisted of pale yellow crystals of mp 62.0–63.0°. Fraction B according to vpc analysis consisted of seven and one-half parts IX and one part VIII. This fraction upon crystallization from 1:2 mixture of methylene chloride and petroleum ether at −78° yielded 1.1 g of crystals of mp 84–86° and, after recrystallization from the same solvent, 0.25 g of white crystals (pure IX) of mp 86.5–87.0°.

Irradiation of 20 ml of dimethyl acetylenedicarboxylate in 307 g of naphthalene at 90° for 7 days in the quartz cell equipped with Pyrex filter gave after the usual work-up 8.0 g of petroleum ether insoluble residue and 2.7 g of petroleum ether soluble product. The latter on approximate vpc analysis on the SE-30 column indicated the following relative amounts—1:3:3:3:1:5—for adducts VI–XI, respectively.

Irradiation of a similar mixture of dimethyl acetylenedicarboxylate and naphthalene containing 5.0 g of benzophenone for 24 hr in the quartz cell at 90° gave according to vpc analysis 0.45 g (1.0%) of VII, 0.44 g (1.0%) of IX, 0.12 g (0.28%) of X, 0.34 g (0.8%) of XI, and only traces of VI and VIII.

B. In Methanol.—A solution of 60 g (0.47 mol) of naphthalene and 20 ml (0.160 mol) of dimethyl acetylenedicarboxylate in 275 ml of hot methanol was placed in the quartz cell which was heated by hot water which was passed through the inner jacket of the cell at such a rate that the solution was kept at gentle reflux through the 60-hr period of irradiation. A duplicate run was made and the combined reaction mixtures were worked up according to the procedure for runs in molten naphthalene. There was obtained 29 g of petroleum ether insoluble residue and 24 g of petroleum ether soluble product. The latter according to analysis by vpc contained 0.68 g (0.79%) of VII, 0.61 g (0.71%) of IX, 0.75 g (0.81%) of X, 6.5 g (7.5%) of XI, and less than 0.05 g of other 1:1 adducts (yields based upon starting dimethyl acetylenedicarboxylate). Chromatography of the petroleum ether soluble product on silica gel after the manner previously described gave 8.5 g of 1:1 adducts. These were dissolved in 25 ml of hot methanol and allowed to crystallize overnight at about 5°. White crystals of XI, 6.13 g (7.1% yield), mp 84.0–85.0°, were isolated by filtration.

In another preparation 20 g of naphthalene and 5.0 ml of dimethyl acetylenedicarboxylate in 300 ml of methanol were irradiated in the quartz cell for 24 hr at 15° while a slow stream of nitrogen bubbled through the solution. The starting materials were removed on a rotary evaporator at 100° (0.1 mm). From ten such runs 14.9 g of nonvolatile residue was obtained. Analysis of the residue by vpc gave 0.38 g (0.32%) of VII, 0.11 g (0.10%) of IX, 0.30 g (0.29%) of X, 0.96 g (0.89%) of XI, and 2.0 g (2.9%) of dimethyl 2-hydroxymethylfumarate. The last compound came prior to adduct VII during vpc analysis. It could be isolated by liquid chromatography on silica gel and was eluted after the adducts VII–XI by 25% acetone in benzene. After a second chromatography on silica gel it was obtained in greater than 99% purity (vpc analysis).

Dimethyl Hydroxymethylfumarate.—This compound was isolated (see above) as a colorless oil from photochemical reactions of dimethyl acetylenedicarboxylate with naphthalene in methanol solution. Irradiation of 5.0 ml of dimethyl acetylenedicarboxylate in 325 ml of methanol in the quartz cell at room temperature for 24 hr under a nitrogen atmosphere gave, according to analysis by vpc, 0.45 g (6.5% yield) of dimethyl hydroxymethylfumarate. This compound was identified by its spectral properties: nmr ($CDCl_3$) τ 3.78 (1.0 H, triplet, J = 1.8 Hz, CH=), 5.70 (2.0 H, doublet, J = 1.8 Hz, CH_2), 6.22 (3.1 H, singlet, CH_3O), 6.30 (3.1 H, singlet, CH_3O). The coupling between the vinyl hydrogen and the methylene group is that expected for a *trans* relationship between these groups.[15] The ir spectrum (neat) had broad OH absorption at 2.75–3.2, broad strong C=O absorption centered at 5.78, and medium C=C absorption at 6.00 μ. This compound arose from the photochemical addition of methanol to dimethyl acetylenedicarboxylate analogous to the photochemical addition of 2-propanol to acetylenedicarboxylic acid.[16]

C. In Cyclohexane.—A solution of 20.0 g (0.0156 mol) of naphthalene and 5.0 ml (0.040 mol) of dimethyl acetylenedicarboxylate was irradiated in the quartz cell under nitrogen for 24 hr at room temperature. The solvent and starting materials were removed *in vacuo* to give 1.33 g of residue which vpc analysis indicated to contain 0.033 g (0.36%) of cyclohexane adducts of dimethyl acetylenedicarboxylate (see below) and <0.07 g of 1:1 adducts of naphthalene and dimethyl acetylenedicarboxylate. These latter were formed in the ratio for VII/IX/X/XI of about 6:1:4:4.

Cyclohexane Adducts of Dimethyl Acetylenedicarboxylate.—A solution of 8.0 ml (0.064 mol) of dimethyl acetylenedicarboxylate in 300 ml of cyclohexane (which had been purified by distillation from concentrated sulfuric acid and then passage through a column packed with activated alumina) was irradiated for 24 hr under nitrogen in the quartz cell. An insoluble product was formed in the cell during irradiation; this (3.6 g) was removed by filtration. The solvent was removed on a rotating evaporator and the yellow viscous residue (7.9 g) was distilled through a modified Hickman still.[35] The first fraction (1.0 g) was mostly unreacted dimethyl acetylenedicarboxylate (vpc analysis) and the second fraction [1.5 g which distilled at a bath temperature of 150–160° (20 mm)] was mostly cyclohexane adducts of dimethyl acetylenedicarboxylate (containing about a 5:1 ratio of the two major components). The second fraction was purified by preparative vpc at 200° on a 6 ft × 0.5 in. column containing 10% polyphenyl ether on Chromosorb. There was obtained 0.76 g of product which by vpc analysis (silicone gum rubber column) consisted of 95% a compound of retention time of 10.5 min with the remainder being a 3:1 mixture of compounds of retention times of 9.7 and 10.0 min: nmr (CCl_4) τ 4.70 (0.84 H, CH=), 6.56 (3.0 H, CO_2CH_3), 6.67 (3.0 H, CO_2CH_3), 7.5–9.2 (11.5 H, C_6H_{11}). The major product is assumed to be dimethyl cyclohexylfumarate and the major impurity dimethyl cyclohexylmaleate.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02; mol wt, 226. Found: C, 63.00, 63.18; H, 7.85, 7.96; mol wt, 241, 242.

D. In Benzene.—A solution of 20.0 g of naphthalene and 5.0 ml of dimethyl acetylenedicarboxylate in 325 ml of benzene was irradiated under nitrogen for 22 hr in the quartz cell at room temperature. After removal of solvents and reactants, finally at 100° (0.1 mm), there remained 1.01 g of residue which contained no more than 0.1 g of 1:1 adducts of naphthalene and dimethyl acetylenedicarboxylate. According to vpc analysis these adducts were formed in the ratio for VII/IX/X/XI of about 0.8:2.7:0.7:1.0. Only a small amount of dimethyl cyclooctatetraene-1,2-dicarboxylate was formed; other experiments showed that as little as 0.52 g of naphthalene in a similar experiment (20-hr irradiation) reduced the yield of this benzene adduct from 15 to 9.8%.

Thermal Reaction of Dimethyl Acetylenedicarboxylate with Naphthalene.—A mixture of 40.0 g (0.310 mol) of naphthalene and 20.0 ml (0.161 mol) of dimethyl acetylenedicarboxylate was sealed in a heavy-walled Pyrex tube and heated in an oil bath at 180–185° for 48 hr. After removal of starting materials on a rotating evaporator at 100° (0.1 mm), 31 g of residue was obtained. The residue was dissolved in 80 ml of chloroform and the solution was poured into 3.5 l. of petroleum ether to give, after filtration and removal of the solvent, 17.6 g of soluble product. The petroleum ether soluble product was chromatographed on 1300 g of Brinkman No. 7734 silica gel. Elution with benzene containing 1–3% ethyl ether gave 7.3 g (17% yield) of crude dimethyl 1,4-dihydro-1,4-ethenonaphthalene-2,3-dicarboxylate (VI), which after one recrystallization from methanol gave 6.1 g of white crystals, mp 75–76°. Further elution with 5% ethyl ether in benzene gave 1.9 g of another substance which after recrystallization from methanol gave white crystals (1.2 g) of mp 118.5–119.0°. This compound had λ_{max}^{EtOH} 277 mμ (ε 14,600), shoulder 250 (9400); nmr ($CDCl_3$) four peaks of equal area at τ 5.73, 6.03, 6.15, and 6.18 attributable to OCH_3. These properties are similar to those reported recently for trimethyl 5-methoxyfuran-2,3,4-tricarboxylate[36] and this structure is confirmed by the following analysis.

Anal. Calcd for $C_{11}H_{12}O_8$: C, 48.5; H, 4.44; mol wt, 272. Found: C, 48.5; H, 4.54; mol wt, 262 (in $CHCl_3$).

Repetition of the above reaction with 35 g of naphthalene, 20.0 ml of dimethyl acetylenedicarboxylate, and 0.25 g of hydroquinone in a sealed tube at 170–180° for 3 days gave, after a similar work-up, 10.7 g (25% yield) of crude VI.

In a reaction which was run to simulate conditions (but in absence of light) of a photochemical reaction with molten naphthalene, 154 g of naphthalene and 10.0 ml of dimethyl acetylenedicarboxylate were heated in a stoppered flask covered with aluminum foil for 7 days in a steam bath. Analysis of the product by vpc indicated the formation of 0.63 g (2.9% yield) of VI.

Dimethyl 1,4-Dihydro-1,4-ethenonaphthalene-2,3-dicarboxylate (VI).—This compound was prepared as above from thermal reaction of dimethyl acetylenedicarboxylate with naphthalene. After two recrystallizations from methanol the compound had mp 77.0–77.5°; λ_{max}^{EtOH} 204 mμ (ε 25,600), 208 (25,300), 238 (16,900), 274 (2160), 283 (2010), 318 (482), 334 (444); nmr ($CDCl_3$) τ 2.7–3.2 (6.1 H, complex multiplet), 4.78 (1.9 H, doublet of doublets, J = 3 and 5 Hz), 6.27 (6.0 H, singlet).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; mol wt, 270. Found: C, 71.47, 71.49; H, 5.38, 5.14; mol wt, 269, 260 (in chloroform).

Hydrogenation of 0.340 g (1.26 mmol) of VI over a 5% palladium-on-charcoal catalyst in ethyl acetate resulted in absorption of 2.05 mol of hydrogen/mol of VI. From the hydrogenation mixture 0.25 g of compound, mp 90.5–91.0° (twice recrystallized from methanol), was recovered: nmr (CCl_4) τ 2.84 (4.2 H, singlet), 6.34 (6.0 H, singlet), 6.70 (2.2 H, multiplet), 7.3 (2.3 H, broad singlet), 7.8 (1.8 H, multiplet), 8.7 (1.8 H, multiplet). These values agree with those reported for *exo*-dimethyl 2,3-benzobicyclo[2.2.2]octane-5,6-dicarboxylate.[18]

Irradiation of Dimethyl 1,4-Dihydro-1,4-ethenonaphthalene-2,3-dicarboxylate (VI).—A solution of 3.00 g (0.011 mol) of VI in 325 ml of methanol was irradiated for 11 hr under a nitrogen atmosphere in the quartz cell equipped with a Pyrex filter between the lamp and cell. Analysis of the product by vpc indicated that 2.4 g (80% yield) of dimethyl benzocyclooctene-7,8-dicarboxylate (VIII) had been formed and the remainder of the volatile product consisted of about an equal mixture of starting material VI and of another product of retention time slightly longer than that of IX. The solvent was removed *in vacuo* and the residue was taken up in 15 ml of hot methanol. A white precipitate (0.13 g) was removed by filtration, washed with methanol, and discarded. The methanol solution and wash liquors were concentrated to 10 ml and kept at 5° overnight. White crystals of VIII, 2.2 g (72% yield), were isolated by filtration and had mp 76.0–77.0°.

In the above run the conversion of VI into VIII was followed by periodic vpc analysis of small portions of the reaction mixture and was terminated when the yield of VIII was near a maximum. Continued irradiation of a similar solution under the same conditions gave increasing amounts of a compound of retention time slightly longer than that of IX, such that after 42 hr this compound made up some 88% of the total volatile product, which also contained small quantities of VI, VIII, and two unknown products of longer retention time. Irradiations in absence of a Pyrex filter appear to be qualitatively similar but proceed much more rapidly.

A solution of 0.54 g of VI in 300 ml of acetone was irradiated for 2.5 hr under a nitrogen atmosphere in the quartz cell equipped with a Pyrex filter. Analysis of the product by vpc gave three compounds in relative amounts of about 5:3:2. The first of these had a retention time near that of VII but was clearly different from this compound (peak broadening on admixture with VII), the second was identical in retention time to IX, while the third component had a retention time intermediate between IX and X.

Dimethyl Benzocyclooctene-7,8-dicarboxylate (VIII).—The synthesis of this compound by irradiation of VI is given above. A product of identical vpc retention time on two columns (silicone gum rubber and Apiezon L) was obtained from irradiation of dimethyl acetylenedicarboxylate in molten naphthalene. The white compound isolated from the former source had mp 77.0–77.5° after a total of three recrystallizations from methanol.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; mol wt, 270. Found: C, 70.96, 71.24; H, 5.27, 5.44; mol wt, 262, 274 (in chloroform).

Hydrogenation of VIII (0.0627 g, 0.232 mmol) in ethyl acetate over a 5% palladium-on-charcoal catalyst resulted in the uptake of 2.9 molar equiv of hydrogen. The recovered hydrogenated liquid ester gave λ_{max}^{EtOH} 209 mμ (ε 9940), 211 (9900), 263 (460), 271 (400); nmr (CCl_4) τ 2.92 (4.0 H, singlet), 6.38 (6.4 H, singlet), 6.7–8.5 (9.2 H, complex multiplets).

Saponification of VIII (1.13 g, 4.2 mmol) with 1.3 g of potassium hydroxide in 20 ml of 95% ethanol at reflux for 15 min gave a lustrous precipitate. The mixture was cooled and the precipitate was separated by filtration. The precipitate was washed with absolute ethanol, dissolved in water, and acidified to pH 2. The bright yellow precipitate was separated by filtration, washed, and dried to give 0.64 g (60% yield) of acid of mp 200–202° dec. A portion (0.10 g) of this acid upon treatment with an ethereal solution of diazomethane regenerated the starting ester VIII (according to melting point and mixture melting point). The remainder upon vacuum sublimation at 20 μ and a bath temperature of 180° for some 24 hr gave 0.51 g of orange-yellow crystals of mp 196.0–197.0°. Treatment of a portion of these with acetic anhydride (reflux temperature, 6 hr) and recrystallization of the dark brown residue from benzene–petroleum ether gave yellow crystals, mp 196.0–197.0° which were indistinguishable (mixture melting point and ir spectral comparisons) from the crystals from vacuum sublimation. The ir spectrum (CCl_4) showed characteristic absorption at 5.42 (s), 5.65 (vs), and 6.07 μ (m) as expected for an unsaturated cyclic anhydride. The compound gave the correct analysis for benzocyclooctene-7,8-dicarboxylic anhydride.

Anal. Calcd for $C_{14}H_8O_3$: C, 75.00; H, 3.60. Found: C, 75.05, 74.94; H, 3.91, 3.86.

Dimethyl 1-Naphthalenefumarate (VII).—This pale yellow compound of mp 62.0–63.0° was separated from the photochemical reaction products of dimethyl acetylenedicarboxylate and molten naphthalene by the procedure already given. The compound had λ_{max}^{EtOH} 223 mμ (ε *ca.* 70,000), 264 (shoulder, 4400), 272 (5430), 281 (5780), and 288 (shoulder, 4670); nmr (CCl_4) at τ 2.2–3.0 (7.8 H, complex multiplet), 6.52 (3.0 H, singlet), and 6.80 (3.0 H, singlet).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; mol wt, 270. Found: C, 71.02, 71.14; H, 5.30, 5.21; mol wt, 272, 268 (in acetone).

Dimethyl 1-Naphthalenesuccinate from VII.—A 0.813-g (3.01 mmol) sample of VII (95% pure *via* vpc analysis, remainder XI) upon hydrogenation in ethyl acetate over 1.8 g of 5% palladium-on-charcoal catalyst absorbed 0.96 molar equiv of hydrogen. After filtration and removal of solvent 0.73 g of crude hydrogenation product was recovered; this was combined with 0.60 g of similar material from another hydrogenation. Chromatography on silica gel with elution with benzene gave a main fraction (1.01 g) which upon recrystallization from methanol amounted to 0.58 g of white crystals of mp 60.0–60.5°; nmr (CCl_4) τ 1.8–2.7 (6.8 H, complex multiplet), 5.12 (0.97 H, doublet of doublets, J = 5.4 and 10.0 Hz), 6.45 (3.0 H, singlet), 6.47 (3.0 H, singlet), 6.70 (0.9 H, doublet of doublets, J = 10.0

(36) E. Winterfeldt and G. Giesler, *Angew. Chem.*, **78**, 588 (1966); C. F. Huebner, E. Donoghue, L. Dorfman, F. A. Stuber, N. Danieli, and E. Wenkert, *Tetrahedron Lett.*, 1185 (1966).

and 17.0 Hz), and 7.42 (1.1 H, doublet of doublets, J = 5.4 and 17.0 Hz).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.54, 70.31; H, 5.80, 5.83.

Dimethyl 1-Naphthalenesuccinate from Dimethyl 1-Naphthalenemaleate.—Arylation of maleic acid with diazotized 1-aminonaphthalene gave according to the procedure of Denivello and Razavi[22] an 11% yield of 1-naphthalenemaleic anhydride, which after recrystallization from benzene–petroleum ether consisted of yellow crystals of mp 115.0–116.0° (lit.[22] mp 116°). Solution of the anhydride in 10% aqueous KOH, acidification to pH 2 with hydrochloric acid, and extraction with ether gave a solution of 1-naphthylmaleic acid which upon reaction with ethereal diazomethane yielded, upon removal of solvent, oily dimethyl 1-naphthalenemaleate. A portion of this material upon hydrogenation in ethyl acetate over a 5% palladium-on-charcoal catalyst gave, after recrystallization from methanol, white crystals of mp 59.0–60.0°. The ir spectrum, mixture melting point, and vpc retention time of this sample of dimethyl 1-naphthalenesuccinate indicated that it was identical with the compound prepared above from hydrogenation of VII. On the other hand, compound VII (dimethyl 1-naphthalenefumarate) had a higher melting point than dimethyl 1-naphthalenemaleate and a shorter vpc retention time (8.7 *vs.* 13.8 min on Apiezon L column at 280°).

Dimethyl 2-Naphthalenemaleate and Dimethyl 2-Naphthalenesuccinate.—These compounds were prepared for comparison with VII and dihydro VII since dimethyl 2-naphthalenesuccinate has a reported[37] melting point of 65°, near that found for dihydro VII. 2-Naphthalenemaleic anhydride was prepared in 20% yield by reaction of diazotized 2-aminonaphthalene with maleic acid according to the procedure of Denivello and Razavi.[22] The bright yellow anhydride (2.0 g), mp 168.0–169.0° (lit.[22] mp 168°), after hydrolysis with aqueous KOH, acidification, extraction with ether, and reaction of the extract with ethereal diazomethane gave 2.1 g of crude dimethyl 2-naphthalenemaleate (mp 78–80°). Recrystallization from methanol gave crystals of mp 80.0–80.5°.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.80, 70.70; H, 5.14, 5.19.

Hydrogenation of dimethyl 2-naphthalenemaleate over 5% palladium on charcoal in ethyl acetate gave, after two recrystallizations from methanol, dimethyl 2-naphthalenesuccinate, mp 63.5–64.0° (lit.[37] mp 65°).

Not only is the melting point of dimethyl 2-naphthalenemaleate much different from that of VII but also the vpc retention time of dimethyl 2-naphthylsuccinate (9.6 min) is longer than that of dihydro VII (dimethyl 1-naphthalenesuccinate, 7.8 min on Apiezon L column at 280°).

Dimethyl 2-Naphthalenefumarate from Dimethyl 2-Naphthalenemaleate.—Irradiation of 1.50 g of dimethyl 2-naphthalenemaleate dissolved in 400 ml of dioxane in a Pyrex cell under nitrogen gave after 1.0 hr 90% isomerization (vpc analysis) to a new product (8.2-min retention time *vs.* 11.4 min for the starting compound on Apiezon L column at 250°). Longer periods of irradiation up to 8 hr did not alter the yield of the photoproduct. The reaction product, after removal of dioxane, was recrystallized from methanol to give 1.2 g of crude crystals. These were combined with 0.5 g of crystals from a similar reaction and the mixture was chromatographed on silica gel with elution by benzene to give, after one recrystallization from methanol, 1.0 g of pale yellow crystals of mp 51.8–52.5°. This product has the expected spectral properties for dimethyl 2-naphthalenefumarate: λ_{max}^{EtOH} 223 mμ (ε 82,700), 267.5 (13,300), 305 (shoulder, 5200), 338 (shoulder, 1700); nmr (CCl_4) τ 2.1–2.8 (6.7 H, multiplet), 3.01 (1.0 H, singlet), 6.26 (3.0 H, singlet), 6.53 (3.0 H, singlet). Hydrogenation of the product (0.49 g, 1.8 mmol) in ethyl acetate over a 5% palladium-on-charcoal catalyst resulted in uptake of 1.8 mmol of hydrogen and gave, after two recrystallizations from methanol, white needles of mp 63.0–63.5°; nmr (CCl_4) τ 2.2–2.8 (7.1 H, complex multiplet), 5.83 (1.0 H, quartet, J = 6 and 10 Hz), 6.39 (6.0 H, singlet), 6.78 (1.0 H, quartet, J = 10 and 16 Hz), 7.38 (1.0 H, quartet, J = 6 and 16 Hz). The hydrogenated photoproduct has identical melting point and ir, nmr, and vpc properties with those of the sample of dimethyl 2-naphthalenesuccinate prepared above by hydrogenation of dimethyl 2-naphthalenemaleate. The photoproduct from dimethyl 2-naphthalenemaleate is accordingly dimethyl 2-naphthalenefumarate. Photoadduct X from naphthalene and dimethyl acetylenedicarboxylate was found to be identical in vpc retention time on the two columns[34] with this sample of dimethyl 2-naphthalenefumarate; also the mixture of crude photoadducts from naphthalene likely contained minor amounts of dimethyl 2-naphthalenemaleate.

Dimethyl 3,4-Benzotricyclo[3.3.0.0^{2,8}]octa-3,6-diene-6,7-dicarboxylate (IX).—This compound was isolated from the photochemical reaction of dimethyl acetylenedicarboxylate with molten naphthalene as described earlier and consisted of colorless crystals of mp 86.5–87.0°.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; mol wt, 270. Found: C, 71.10, 70.97; H, 5.07, 5.20; mol wt, 271, 274 (in benzene).

Hydrogenation of IX (0.156 g, 0.577 mmol) in glacial acetic acid in presence of 1.0 g of 5% palladium on charcoal resulted in uptake of 2.03 molar equiv of hydrogen. Analysis of the hydrogenated product by vpc on the Apiezon L column at 260° indicated that a 1:3 mixture of two compounds were formed having retention times of 8.9 and 9.4 min, respectively, compared with 8.5 min for IX.

Saponification of IX (0.40 g) by heating with 0.70 g of potassium hydroxide in 15 ml of methanol at reflux for 30 min, evaporation of most of the solvent on the steam bath, acidification to pH 2 with 6 N HCl, and extraction with ether gave an ethereal extract which yielded a viscous liquid hardening to a glass. Attempts to recrystallize the acidic product from common solvents were unsuccessful. A portion was esterified with ethereal diazomethane and analysis by vpc (Apiezon L column at 260°) indicated that a 3:1 mixture of IX and an unknown ester (of retention times 8.5 and 9.0 min, respectively) were present.

An attempted deuterium exchange upon IX (0.31 g, 1.6 mmol) with 1.7 mmol of $NaOCH_3$ in 5 ml of CH_3OD at reflux temperature for 48 hr gave upon work-up a product of unchanged nmr spectrum from starting IX (therefore, absence of hydrogens α to the carbomethoxyl groups is implied; *cf.* adduct XI).

Irradiation of 0.225 g of IX in 325 ml of methanol in the quartz cell under nitrogen for 1 hr gave, after recrystallization from methanol, 0.217 g of colorless crystals which were identical in melting point, mixture melting point, and vpc retention time with starting IX.

Oxidation of 0.318 g (1.18 mmol) of IX was effected with 1.09 g (0.69 mmol) of $KMnO_4$ in 20 ml of purified acetone, 10 ml of water, and 0.10 ml of glacial acetic acid overnight at room temperature. After addition of a little sodium bisulfite, manganese dioxide was removed by filtration and the precipitate was washed well with water and acetone. The combined filtrate and wash liquors were evaporated to dryness *in vacuo*. The residue was taken up in a little water, filtered to remove a trace of precipitate, acidified to pH 2, and extracted with ether. The ether extract after drying over anhydrous Na_2SO_4 and removal of ether gave 0.150 g of residue. This was esterified with excess diazomethane and vpc analysis (Apiezon L column) of the ester indicated the presence of 0.125 g (55% yield) of dimethyl phthalate and small amounts of three unknown products of retention times 5.6, 9.8, and 11.0 min (retention time of IX, 8.5 min).

Dimethyl *trans*-Acenaphthene-1,2-dicarboxylate (XI).—This compound is the major adduct from photolysis of dimethyl acetylenedicarboxylate with naphthalene in methanol at 65° and was isolated from this reaction in the manner previously described. After a total of three recrystallizations from methanol, white crystals of mp 84.5–85.0° were obtained. This compound was identical in vpc retention time on two columns (Apiezon L and silicone gum rubber) with one of the adducts from the photochemical reaction of dimethyl acetylenedicarboxylate with molten naphthalene. The compound has λ_{max}^{EtOH} 226 mμ (ε 84,800), 267 (3840), 277 (6480), 287 (7690), 291 (5690), 298 (5150), 304 (1790), 315 (663), 319 (431).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; mol wt, 270. Found: C, 71.02, 71.18; H, 5.36, 5.43; mol wt, 270, 266 (in acetone).

An attempted hydrogenation of XI (0.0711 g, 0.26 mmol) in 5 ml of glacial acetic acid over 0.52 g of 5% palladium on charcoal resulted in absorption of less than 0.06 mmol of hydrogen in the normal time (1 hr) for complete hydrogenation of the other adducts.

Compound XI (0.27 g, 1.0 mmol) was dissolved in 1 ml of $CDCl_3$ and 0.5 ml of CH_3OD in an nmr tube. The region at τ 4.95 was swept through immediately and again after 10 min with

(37) W. H. Linnel, D. W. Matheson, and D. T. Modi, *J. Chem. Soc.*, 3257 (1953).

no change in the spectrum. A 0.05-ml portion of a solution of 0.25 g of CH_3ONa in 0.50 ml of CH_3OD was added to the nmr tube and the spectrum was swept through at intervals. There was a rapid decrease in the peak at τ 4.95; after 20 min this peak was reduced to 8% of its original area. The other nmr peaks of XI were unchanged. In another experiment 0.615 g (2.28 mmol) of XI was dissolved in 8 ml of CH_3OD containing 0.39 g (7.2 mmol) of $NaOCH_3$ and the solution was heated at reflux for 48 hr with exclusion of moisture. The solvent was removed *in vacuo*, the residue was dissolved in 5 ml of deuterium oxide, and the solution was made acidic with 2 ml of 25% D_2SO_4. The solution was extracted with ether and the ethereal extract dried over anhydrous Na_2SO_4 and then treated with diazomethane (to esterify any saponified ester). From the ethereal solution was isolated 0.555 g of residue which was at least 98% XI according to vpc analysis. Recrystallization of the residue from methanol gave 0.37 g of crystals of the same melting point and mixture melting point as those of the starting ester. The nmr spectrum showed that the absorption at τ 4.95 had been reduced to 11% of its starting peak area.

Adduct XI (1.20 g, 4.45 mmol) was saponified in 15 ml of 95% ethanol containing 2.0 g of potassium hydroxide on a steam bath for 5 min. The potassium salt which precipitated was separated by filtration and washed with 95% ethanol. The salt was dissolved in 10 ml of hot water and the cooled solution was acidified to pH 2 with 6 *N* hydrochloric acid. The acid was separated by filtration, washed with water, and dried overnight at 115° to give 1.05 g of acid of mp 205–208° dec. A small portion of this acid was treated with excess diazomethane in ether and the product was analyzed by vpc. Only the starting ester XI was found.

A 0.968 g (4.00 mmol) sample of the above acid from XI was dissolved in 25 ml of dry pyridine and heated to 70° in a hot-water bath. To this solution was added 2.00 g (4.4 mmol) of lead tetraacetate; there was an immediate evolution of gas for about 30 sec. The solution was heated for 5 min at 70° and then solvent was removed *in vacuo* on a rotary evaporator at a bath temperature at or below 70°. The residue was treated with 20 ml of 2.5 *N* hydrochloric acid. The lead salts were removed by filtration and washed with ether. The aqueous solution was extracted with ether and combined with the ether wash solution. The ethereal solution was washed three times with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. The ether was removed on a rotary evaporator to give 0.239 g of residue. Analysis of the residue on the Apiezon L column indicated that 0.126 g (21% yield) of acenaphthylene had been formed. The residue was chromatographed on 100 g of Brinkman No. 7734 silica gel with elution by petroleum ether which removed a yellow band in the first fraction. The solvent was removed and the yellow residue (0.097 g) was recrystallized from 95% ethanol to give 0.047 g of yellow crystals of mp 90.0–91.0°. A mixture melting point with an authentic sample of Aldrich Chemical Co. acenaphthylene (mp 90.5–91.3°) showed no depression and the ir spectra of the two samples were identical.

A 0.35-g sample of the acid from ester XI was heated at reflux for 48 hr with 10 ml of acetic anhydride. After removal of the solvent *in vacuo*, a black tarry residue remained. Analysis of this residue by vpc using the Apiezon L column at 290° gave no volatile product within 25 min; under these conditions 1-naphthalenemaleic anhydride has a retention time of 8.1 min.

Di-N-benzylamide of *trans*-Acenaphthene-1,2-dicarboxylic Acid.—A 0.54-g (2.00 mmol) sample of ester XI was dissolved in 5 ml of benzylamine and the solution was heated at 175° for 2 hr. The mixture was cooled to room temperature and filtered. The filter cake was washed with cold acetone to give 0.33 g of white needles, mp 257–259°; recrystallization from acetonitrile gave 0.25 g of needles of mp 259.0–260.0°. In early phases of the present work the same crystalline di-N-benzylamide was isolated by reaction of benzylamine upon crude oily photoadducts from the reaction of naphthalene and dimethyl acetylenedicarboxylate in methanol. The compound had λ_{max}^{EtOH} 227 mμ (ε 76,000), 269 (shoulder, 5400), 278.5 (8300), 288.5 (10,200), 292.5 (shoulder, 8000), 300 (6200), 306 (3120), 316.5 (980), 320 (830); nmr (CF_3CO_2H) τ 1.9–2.7 (16.2 H, complex multiplet with some 10 H at 2.63), 4.94 (2.1 H, singlet), 5.38 (4.0 H, doublet, J = 5 Hz). In CF_3CO_2D the hydrogens at τ 5.38 became a singlet; these hydrogens are benzylic hydrogens which in trifluoroacetic acid are split by the adjacent amide hydrogens.

Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.62, 79.79; H, 5.39, 5.48; N, 6.73, 6.57.

The nmr spectrum of this N-benzylamide was unchanged on standing for 8 months at room temperature in trifluoroacetic acid solution. The solution was evaporated to dryness at room temperature and on recrystallization of the residue from acetonitrile gave some 50% recovery of crystals of mp 260.4–261.3°.

Di-N-benzylamide of Naphthalene-2,3-dicarboxylic Acid.—The dimethyl ester of naphthalene-2,3-dicarboxylic acid of mp 47–49° (1.0 g) upon reaction with 6 ml of benzylamine containing 0.2 g of NH_4Cl at 178° for 2.7 hr gave, following the usual work-up and recrystallization from aqueous ethanol and then acetonitrile, 1.1 g of white crystals of mp 203°; λ_{max}^{EtOH} 233 mμ (ε 78,000), 268 (shoulder, 8770), 278 (shoulder, 7000), 316 (730), 329 (820); nmr (CF_3CO_2H) τ 1.25 (2.0 H, broad peak which disappeared in CF_3CO_2D), 1.7–2.6 (16.5 H complex multiplet, ~10 H at 2.57), 5.26 (3.9 H, singlet).

N-Benzylimide of Naphthalene-2,3-dicarboxylic Acid.—The di-N-benzylamide of naphthalene-2,3-dicarboxylic acid upon standing overnight at room temperature in CF_3CO_2D showed the appearance of new nmr absorption at τ 1.52, 1.88, 4.87, 5.06, and 5.56. A solution of 0.30 g of the di-N-benzylamide which had stood for 8 months in 1.2 ml of CF_3CO_2D was evaporated to dryness at room temperature and the residue recrystallized from aqueous ethanol to give 0.11 g of white crystals; after another recrystallization from ethanol, these had mp 211.0–212.0°. Whereas the starting di-N-benzylamide had λ_{max}^{KBr} 3.09 (NH), 6.15 and 6.54 μ (C=O), the present compound lacks NH absorption and has carbonyl absorption at 5.67 and 5.90 μ as expected for a cyclic N-benzylimide.

Anal. Calcd for $C_{19}H_{13}O_2N$: C, 79.43; H, 4.56; N, 4.87. Found: C, 79.69, 79.50; H, 4.39, 4.50; N, 5.01, 4.96.

Dimethyl *trans*-Acenaphthene-1,2-dicarboxylate (XI) from Photolysis of Dimethyl 1-Naphthalenefumarate (VII).—A solution of 0.800 g of dimethyl 1-naphthalenefumarate (VII) in 200 ml of methanol was irradiated at room temperature in the quartz cell with use of a Pyrex filter under a nitrogen atmosphere for 11 hr. Removal of the solvent *in vacuo* gave 0.794 g of residue which according to analysis by vpc (Apiezon L column) contained 0.025 g of unreacted VII and 0.47 g (59% yield) of dimethyl *trans*-acenaphthene-1,2-dicarboxylate; no other compounds of comparable volatility were detected in the vpc trace. The residue was recrystallized from methanol to give 0.38 g of white crystals of mp 83.5–84.0° (mixture melting point with dimethyl *trans*-acenaphthene-1,2-dicarboxylate XI from irradiation of naphthalene with dimethyl acetylenedicarboxylate in methanol showed no depression).

Dimethyl *trans*-Acenaphthene-1,2-dicarboxylate (XI) from Photolysis of Dimethyl 1-Naphthalenemaleate.—Crude dimethyl 1-naphthalenemaleate (2.1 g, prepared by esterification of 1-naphthalenemaleic anhydride[22] with methanol–sulfuric acid, but which according to vpc analysis was 75% pure and contained some 20% unreacted anhydride) was dissolved in 265 ml of methanol and irradiated for 8 hr in the quartz cell. Removal of solvent *in vacuo* gave a dark residue which was chromatographed on 100 g of Brinkman No. 7734 silica gel. The first fraction (elution with 300 ml of 2% ether in benzene) after removal of solvent amounted to 0.85 g and after crystallization from methanol gave 0.55 g of crystals, mp 75–77°. After two more recrystallizations from methanol, white crystals (mp 82.5–83.0°) were obtained which were identical in ir, uv, and nmr spectral comparisons and gave no mixture melting point depression with dimethyl *trans*-acenaphthene-1,2-dicarboxylate (XI) obtained from photochemical reaction of naphthalene with dimethyl acetylenedicarboxylate. A repetition of this experiment with a pure sample of dimethyl 1-naphthalenemaleate (0.900 g) in 200 ml of methanol with irradiation for 13 hr through a Pyrex filter under a nitrogen atmosphere gave 0.67 g (74% yield) of dimethyl *trans*-acenaphthene-1,2-dicarboxylate according to vpc analysis (Apiezon L column).

Irradiation of 0.456 g of dimethyl 1-naphthalenemaleate (97.4% pure *via* vpc analysis) in 150 ml of anhydrous dioxane in the quartz cell with a Pyrex filter under a nitrogen atmosphere gave after 8 hr of irradiation a 92.5% yield (vpc analysis of dimethyl *trans*-acenaphthene-1,2-dicarboxylate). This reaction was followed throughout the irradiation by withdrawal of small samples for vpc analysis. After 10 min of irradiation, 42% dimethyl 1-naphthalenefumarate, 15% dimethyl 1-naphthalenemaleate, and 39% dimethyl *trans*-acenaphthene-1,2-dicarboxylate were present; after 60 min these yields were respectively 10, 1.2, and 75%.

Registry No.—Dimethyl acetylenedicarboxylate, 762-42-5; benzene, 71-43-2; naphthalene, 91-20-3; VI, 19981-73-8; VII, 19988-65-9; VIII, 19988-66-0; VIII (hydrogenated), 19981-74-9; IX, 19981-75-0; XI, 19988-67-1; dimethyl cyclooctatetraene-1,2-carboxylate, 15956-91-9; cyclooctatetraene-1,2-dicarboxylic acid, 13753-01-0; dimethyl hydroxymethylfumarate, 19988-68-2; dimethyl cyclohexylfumarate, 19988-69-3; benzocyclooctene-7,8-dicarboxylic anhydride, 19981-78-3; dimethyl 1-naphthalenesuccinate, 19981-79-4; dimethyl 2-naphthalenemaleate, 19988-70-6; dimethyl 2-naphthalenefumarate, 19988-71-7; *trans*-acenaphthene-1,2-dicarboxylic acid (di-N-benzylamide), 19988-72-8; naphthalene-2,3-dicarboxylic acid (di-N-benzylamide), 19981-80-7; naphthalene-2,3-dicarboxylic acid (N-benzylimide), 20013-26-7.

Acknowledgment.—The support of this work by the U. S. Army Research Office (Durham) under Grant No. DA-ARO(D)-31-124-G258, by the National Aeronautics and Space Administration Grant NsG-657, and by the National Science Foundation (GP-8309) is gratefully acknowledged.

The Synthesis and Properties of Germanium Peroxides and Hydroperoxides[1]

RALPH L. DANNLEY AND GEORGE C. FARRANT

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received July 8, 1968

Triphenylgermyl, diphenyl-*p*-trifluoromethylphenylgermyl, diphenyl-*p*-methoxyphenylgermyl, and tricyclohexylgermyl hydroperoxides and bis(diphenyl-*p*-trifluoromethylphenylgermyl) peroxide have been sythesized from the corresponding organogermanium halides, hydroxides, oxides, methoxides, or amines. The infrared, pmr, and mass spectra are consistent with the proposed structures. Treatment of all of the germyl hydroperoxides or peroxides except *p*-methoxyphenyldiphenylgermyl hydroperoxide with hydrogen chloride yielded the corresponding chlorides in essentially quantitative yields. The *p*-methoxyphenyl group was partially cleaved from germanium upon treatment with hydrogen chloride to produce diphenylgermanium dichloride and anisole.

As a continuation of the studies of the hydroperoxides and peroxides of the group IVb elements,[2-5] representative germanium derivatives of this type have now been synthesized and their chemical and physical properties investigated.

Although several unsymmetrical peroxides containing the GeOOC structure[6,7] and three bisgermyl peroxides have been described,[7-9] the corresponding hydroperoxides had not been synthesized until the preliminary announcement of the preparation of triphenylgermyl hydroperoxide.[5] The present work was undertaken to synthesize a series of germanium hydroperoxides, add to the list of known bisgermyl peroxides, and to determine the physical and chemical properties of these compounds.

Results

The hydroperoxides were synthesized by either a direct nucleophilic displacement of a hydroxy or methoxy group by 98% hydrogen peroxide (method I)

$$R_3GeY + H_2O_2 \longrightarrow R_3GeOOH + HY \qquad (I)$$
$$Y = OH, OCH_3, OGe(C_6H_5)_3$$

or by displacement of a halide by hydrogen peroxide in the presence of anhydrous ammonia (method IIa).

$$R_3GeX + H_2O_2 \xrightarrow{NH_3} R_3GeOOH + NH_4X \qquad (IIa)$$

The bisgermyl peroxides were synthesized by the reaction of a stoichiometric amount of hydrogen peroxide with a triarylhalogermane in the presence of ammonia (method IIb). The yields, methods of synthesis, and analyses are given in Table I.

$$2R_3GeX + H_2O_2 \xrightarrow{NH_3} R_3GeOOGeR_3 + 2NH_4X \qquad (IIb)$$
$$X = Cl, Br$$

The structures of the peroxidic compounds were confirmed by physical methods as well as by elemental and active oxygen analyses. The infrared spectra of the hydroperoxides show a strong absorption in the 3570–3200-cm^{-1} region, indicative of the OH structure. The exchangeable proton in the pmr absorption spectra of the hydroperoxides in deuteriochloroform, listed in Table II, absorbs at very low-field strength, *ca.* δ 7.50. This is similar to the δ 7.8 value for the hydroperoxy proton of *t*-butyl hydroperoxide. Since the hydroxy proton of triphenylgermanol absorbs at δ 1.43 in deuteriochloroform, the low downfield absorptions of the triphenylgermyl hydroperoxide indicates that its exchangeable proton must be attached to the highly electronegative peroxy unit.

The molecular weight of triphenylgermyl hydroperoxide determined by vapor phase osmometry, employing benzene as solvent, was found to be 359 ± 12 for a 0.054 *M* solution, 325 ± 12 for a 0.017 *M* solution, and 323 ± 13 for a 0.0060 *M* solution. Since the molecular formula requires 336, these results indicate that there is a slight degree of association of the hydroperoxide in this solvent as the concentration is increased.

(1) (a) Supported by the U. S. Army Research Office (Durham) through Grant No. DA-ARO (D)-31-124-G720. (b) Taken in part from the dissertation of G. C. Farrant submitted in Jan. 1968 to the Graduate School of Case Western Reserve University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (c) Presented in part at the first Central Regional Meeting of the American Chemical Society, Akron, Ohio, May 10, 1968.

(2) R. L. Dannley and G. Jalics, *J. Org. Chem.*, **30**, 2417 (1965).
(3) R. L. Dannley and G. Jalics, *ibid.*, **30**, 3848 (1965).
(4) R. L. Dannley and W. A. Aue, *ibid.*, **30**, 3845 (1965).
(5) R. L. Dannley and G. Farrant, *J. Amer. Chem. Soc.*, **88**, 627 (1966).
(6) A. G. Davies and C. D. Hall, *J. Chem. Soc.*, 3835 (1959).
(7) A. G. Davies and C. D. Hall, *Chem. Ind.* (London), 1695 (1958).
(8) A. Rieche and J. Dahlmann, *Angew. Chem.*, **73**, 494 (1961).
(9) A. Rieche and J. Dahlmann, *Ann.*, **675**, 19 (1964).

TABLE I

PREPARATION AND ANALYSIS OF ORGANOGERMANIUM HYDROPEROXIDES AND PEROXIDES

Product	Registry no.	Starting reagent	Method of prepn	% yield	Mp, °C (n^{25}D)	Recrystn solvent	Calcd, %				Found			
							C	H	Ge	Active oxygen	C	H	Ge	Active oxygen
$(C_6H_5)_3GeOOH$	5274-38-4	$(C_6H_5)_3GeCl$	IIa	60	137.5–138.0	Ether	64.17	4.79	17.92	4.76	64.39	4.76	17.91	4.75
$(C_6H_5)_3GeOOH$		$(C_6H_5)_3GeBr$	IIa	55	137.5–138.0	Ether								
$(C_6H_5)_3GeOOH$		$(C_6H_5)_3GeOH$	I	60	137.5–138.0	Ether								
$(C_6H_5)_3GeOOH$		$[(C_6H_5)_3Ge]_2O$	I	65	137.5–138.0	Ether								
p-$CF_3C_6H_4(C_6H_5)_2GeOOH$	19987-82-7	p-$CF_3C_6H_4(C_6H_5)_2GeCl$	IIa	42	81.0–81.5	Ether	56.40	3.74	17.92	3.90	56.33	3.97	17.91	3.96
p-$CH_3OC_6H_4(C_6H_5)_2GeOOH$	19987-83-8	p-$CH_3OC_6H_4(C_6H_5)_2GeOCH_3$	I	98	(1.6237)		62.40	4.95	19.75	4.37	62.28	5.10	19.54	4.32
$(C_6H_{11})_3GeOOH$	19987-84-9	$(C_6H_{11})_3GeCl$	IIa	65	180–182 dec	Pentane	60.70	9.65	20.40	4.35	61.05	9.76	20.16	4.30
$[(C_6H_5)_3GeO]_2$	5695-57-8	$(C_6H_5)_3GeCl$	IIb	60	147–148	Pentane–ether (1:1)	67.22	4.70	22.60	2.50	67.45	4.72	22.40	2.45
$[p$-$CF_3C_6H_4(C_6H_5)_2GeO]_2$	19987-86-1	p-$CF_3C_6H_4(C_6H_5)_2GeCl$	IIb	57	134–137	Pentane–ether (1:1)	58.95	3.64		2.07	58.89	3.71		2.05

The mass spectrum of triphenylgermyl hydroperoxide taken at 70 eV shows peaks at 334, 336, 337, 338, and 340 mass units, corresponding to the molecular ions expected from the five stable isotopes of germanium.

Reaction with Hydrogen Chloride.—All of the hydroperoxides, except diphenyl-*p*-methoxyphenylgermyl hydroperoxide, reacted with hydrogen chloride at 25° within 10 min to produce the corresponding triorganogermanium chloride and hydrogen peroxide in better than 98% yield (glpc). There was no rearrangement accompanying this reaction and it therefore obeyed the given stoichiometric equation. No diphenylgermanium dichloride or benzene was found in the acid-treated solutions although yields as low as 0.1 mol % could be detected.

$$R_3GeOOH + HCl \longrightarrow R_3GeCl + H_2O_2$$

Diphenyl-*p*-methoxyphenylgermyl hydroperoxide, on the other hand, when similarly treated with hydrogen chloride, formed diphenylgermanium dichloride and anisole as well as the monochloride in roughly equal amounts. The fact that neither *p*-methoxyphenol nor phenol were formed means that the primary reaction involved the displacement of the germanium oxygen bond to form the monochloride. A secondary reaction involved the cleavage of the anisyl group from either the newly formed monochloride or from the unreacted hydroperoxide. This contention is supported by the fact that high yields of anisole and diphenyldichlorogermane were formed when a 0.05 *M* solution of the monochloride was treated with anhydrous hydrogen chloride under the same conditions. All attempts to

$$p\text{-}CH_3OC_6H_4(C_6H_5)_2GeOOH + HCl \longrightarrow p\text{-}CH_3OC_6H_4(C_6H_5)_2GeCl + H_2O_2$$

$$p\text{-}CH_3OC_6H_4(C_6H_5)_2GeCl + HCl \longrightarrow (C_6H_5)_2GeCl_2 + CH_3OC_6H_5$$

convert this hydroperoxide into its monochloride by reducing the contact time with hydrogen chloride resulted either in incomplete conversion to the monochloride or a substantial amount of cleavage of the anisyl group. Since the *p*-methoxyphenyl group has been shown to cleave some 400–500 times as readily as the phenyl group in the reaction of aryltriethylgermanes with mineral acids,[10] the cleavage of the anisyl group in the present system is not surprising.

The symmetrical bisperoxides prepared during this study also formed the triorganochlorogermanes in better than 97% yield when treated with hydrogen chloride. As in the case of hydroperoxides, no rearrangement occurred during the course of the reaction. These results corroborate the findings of Rieche and Dahlmann,[9] who found that the unsymmetrical carbon germanium peroxides undergo primary oxygen–metal cleavage with hydrogen chloride and not the acid-catalyzed heterolysis of the peroxy bond.

Discussion

The syntheses of the germyl hydroperoxides from hydrogen peroxide and the germanols, germanium oxides, or germanium methoxides are probably simple nucleophilic displacements. The resultant equilibria

(10) (a) C. Eaborn and K. C. Pande, *J. Chem. Soc.*, 297 (1961); (b) C. Eaborn and K. C. Pande, *ibid.*, 5082 (1961); (c) C. Eaborn and K. C. Pande, *ibid.* 1566 (1960).

TABLE II
THE PMR SPECTRAL ABSORPTIONS OF ORGANOGERMYL HYDROPEROXIDES[a]

Compd	Hydroperoxy proton	Aromatic protons	Aliphatic protons
$(C_6H_5)_3GeOOH$	7.64 (S)	7.20–7.85 (M)	
$CH_3OC_6H_4(C_6H_5)_2GeOOH$	7.50 (S)	6.55–7.60 (M)	3.79 (S)
$CF_3C_6H_4(C_6H_5)_2GeOOH$	7.70 (S)	6.55–7.60 (M)	
$(C_6H_{11})_3GeOOH$	7.24 (S)		1.0–2.4 (M)

[a] The spectra were taken on a Varian A-60 nuclear magnetic resonance spectrometer. The solvent was deuteriochloroform (5–10% solutions). The chemical shifts were measured in parts per million from internal TMS: S = singlet, M = multiplet.

are shifted in the proper direction by the excess of hydrogen peroxide, as well as its lower volatility compared with the water or methanol, which is preferentially removed by evaporation. When both the starting material and the final product are liquids, as in the case of the diphenyl-*p*-methoxyphenylgermyl derivative, Table II, the hydroperoxide can be obtained in high yield. However, when the reactants and products are solids, good contact with the hydrogen peroxide is not achieved and the hydroperoxide is of low purity and must be purified by recrystallization. This reduces the yield and method II is preferred.

The mechanism of the formation of triarylgermyl hydroperoxides from the corresponding triarylhalogermane using ammonia as the catalyst (method IIa) is possibly identical with the analogous formation of triorganosilyl hydroperoxides.[2] In the absence of hydrogen peroxide, triarylgermanium amines are rapidly and quantitatively formed. Subsequent displacement of the amide ion by hydrogen peroxide or its anion would lead to the formation of the hydroperoxide. Displacement of the amide ion by triarylgermyl hydroperoxide or its anion would lead to the formation of the symmetrical bisperoxide (method IIb). Undoubtedly there were other reactions occurring in solution many of which were reversible in nature. The position of equilibrium in these reactions depends upon both the electronic and steric effects in the molecules. Hence, in order to prepare a specific hydroperoxide or peroxide different reaction conditions often had to be used.

Although the order of addition of hydrogen peroxide and ammonia was unimportant for the successful synthesis of the triarylgermyl hydroperoxides or peroxides, it was extremely important for the preparation of tricyclohexylgermyl hydroperoxide. When ammonia was bubbled into an ethereal solution of tricyclohexylchlorogermane at 0°, the precipitation of ammonium chloride was very slow and was complete only after 15 or 20 min. However, when the reaction was carried out in the presence of hydrogen peroxide, the precipitation of ammonium chloride was immediate. This indicates that the main reaction sequence involved the nucleophilic displacement of the chloride by the hydroperoxy anion according to the given equations. The

$$NH_3 + H_2O_2 \rightleftharpoons NH_4OOH \rightleftharpoons NH_4^+ + {}^-OOH$$

$$(C_6H_{11})_3GeCl + {}^-OOH \longrightarrow (C_6H_{11})_3GeOOH + Cl^-$$

formation of the germyl amine as an intermediate is not excluded but it can only be a competing reaction. The small steric requirements of the peroxy anion make it the species likely to attack the germyl chloride substituted by the bulky cyclohexyl groups. Steric effects of the alkyl groups have been proved to be of principle importance in other reactions of germyl derivatives. Thus triethyl- and tri-*n*-propylgermanol lose water readily to form the symmetrical oxide while the triisopropylgermanol loses water only slowly below 200° [11] and tricyclohexylgermanol does not form the symmetrical oxide.

All efforts to prepare diphenyl-*p*-methoxyphenylgermyl hydroperoxide from the corresponding germanium chloride using method II met with failure. It is likely that the germanium amine formed, for ammonium chloride precipitated rapidly and quantitatively when the chloride was treated with ammonia. Apparently the hydroperoxide was formed, but underwent a base-catalyzed decomposition prior to its isolation, for only oils of limited active oxygen could be obtained. However, it was found that diphenyl-*p*-methoxyphenylgermyl hydroperoxide could be prepared pure and in very high yield by displacing the methoxy group of the corresponding methoxide with hydrogen peroxide (method I). The hydroperoxide prepared in this manner contained more than 95% of the theoretical active oxygen content. Attempts to crystallize the material always resulted in oils of decreased active oxygen content. However, the material gave the correct elemental analysis, and its infrared and pmr spectra were consistent with the above structural assignment (Table II).

Experimental Section

A number of germanium-containing reagents and reference compounds were prepared and are listed in Table III. The monosubstituted tri-arylhalogermanes were prepared by addition of an arylmagnesium bromide to diphenyldichlorogermane. Since the resulting products were found to be mixtures of the corresponding germyl bromides and chlorides, conversion into the pure halide was achieved by hydrolyzing each crude reaction mixture to the germyl hydroxide or oxide and then treating this with either hydrogen chloride or hydrogen bromide.

Organohalogermanes.—Triphenylchlorogermane, triphenylbromogermane, diphenyldichlorogermane, and tricyclohexylchlorogermane were purchased from either Metallomer Laboratories or Alfa Inorganics, and were used without further purification. The unsymmetrically substituted organohalogermanes prepared during this study were synthesized either by a Grignard arylation of an appropriate diphenyldichlorogermane or phenyltrichlorogermane or reaction of a chloroform solution of the corresponding organogermanium hydroxide (or oxide) with hydrogen chloride or hydrogen bromide. Since the Grignard reaction was most often used, the synthesis of diphenyl-*p*-trifluoromethylchlorogermane will be described. It also illustrates the method used for the synthesis of the other organohalogermanes.

Diphenyl-*p*-trifluoromethylphenylchlorogermane.—*p*-Trifluoromethylphenylmagnesium bromide was prepared by adding *p*-trifluoromethylbromobenzene (16.9 g, 75 mmol) to magnesium turnings (2.00 g, 82 mmol) in anhydrous ether (100 ml). The solution separated into two phases, both of which were slowly added to a boiling solution of diphenyldichlorogermane (22.2 g, 76 mmol) in dry toluene (600 ml). The Grignard solution was added at such a rate that the ether distilled without flooding the condenser. When all of the Grignard reagent had been added and the ether removed by distillation, the resulting purple solution was refluxed at 110° for 18 hr. The solution was concen-

(11) H. H. Anderson, *J. Amer. Chem. Soc.*, **75**, 814 (1953).

TABLE III
PROPERTIES AND ELEMENTAL ANALYSES OF ORGANOGERMANIUM REFERENCE COMPOUNDS

Compd	Registry no.	Mp, °C	Bp (mm), °C	Calcd, %				Found, %			
				C	H	Ge	Cl or Br	C	H	Ge	Cl or Br
p-$CF_3C_6H_4(C_6H_5)_2GeCl$	19987-87-2	54–55	150–159 (0.40)	55.58	3.47	17.82	7.52	55.80	3.52	18.08	7.52
p-$CF_3C_6H_4(C_6H_5)_2GeBr$	19987-88-3	67.0–68.5		50.20	3.13	16.10	17.71	50.24	2.81	15.97	17.93
p-$CH_3OC_6H_4(C_6H_5)_2GeCl$	19987-89-4	80.0–81.5	185–190 (0.025)	61.82	4.65	19.68	9.35	61.65	4.52	19.41	9.61
p-$CH_3OC_6H_4(C_6H_5)_2GeBr$	19987-90-7	75–76		55.30	4.15	17.55	19.29	55.30	4.27	17.32	19.22
p-$CH_3OC_6H_4(C_6H_5)_2GeOH$	19987-91-8	77.5–80.5		65.00	5.17	20.68		64.98	5.20	20.47	
$[p$-$CH_3OC_6H_4(C_6H_5)_2Ge]_2O$	19987-92-9	107		67.14	5.02	21.30		67.41	5.07	21.14	
$[p$-$CF_3C_6H_4(C_6H_5)_2Ge]_2O$	19987-93-0	133		60.30	3.59	19.15		60.51	3.72	18.91	
p-$CH_3OC_6H_4(C_6H_5)_2GeOCH_3$[a]	19987-94-1		185–187 (0.20)	65.61	5.65	19.81		65.64	5.62	19.65	

[a] $n^{25}D$ 1.6062.

trated to approximately 200 ml and then filtered. The semisolid precipitate was dissolved in 200 ml of 3 N hydrochloric acid. The acidic solution was extracted with two 100-ml portions of benzene and the extracts were combined with the filtrate from the previous step. When the solvents were removed from the combined solution by evaporation under reduced pressure, a brown oil remained which was shown by glpc to contain diphenyl-p-trifluoromethylphenylchlorogermane and diphenyl-p-trifluoromethylphenylbromogermane as the two major components in a ratio of approximately 1:2. The crude material was then dissolved in ether (200 ml) and ammonia bubbled under the surface until no more ammonium halide precipitated. The solution was washed two times with 100-ml portions of water and the organic phase was separated and dried over magnesium sulfate. The dried solution was filtered, dried with magnesium sulfate, and the solution then was treated with anhydrous hydrogen chloride to convert the organogermanol into the organochlorogermane. The solvent was removed under vacuum, leaving a dark brown oil (20 g) which was shown by glpc to be the desired product contaminated with approximately 10% diphenyldichlorogermane. The crude liquid was distilled at reduced pressure through a short-path distillation column and the fraction boiling at 150–159° (0.40 mm) (17.2 g, 56% yield) solidified upon standing to give white crystals which melted at 54–55°. The infrared spectrum showed a band at 829 cm^{-1}, indicating *para* substitution.

Organogermanols.—The organogermanols were prepared by the following general procedure. Into a solution of ether (100 ml) and the triorganohalogermane (2.5 mmol) was introduced ammonia gas until no more ammonium halide precipitated. The solution was then washed three times with 20-ml portions of water and the organic phase separated and dried over magnesium sulfate. The ether was removed under reduced pressure and the residue then recrystallized. Triphenylgermanol, when recrystallized from hexane–ether, had mp 134° (lit.[12] mp 132.2°). Tricyclohexylgermanol, when recrystallized from heptane, had mp 176° (lit.[13] mp 176–177°).

Organogermanium Oxides.—The triorganogermanium oxides were synthesized according to the following procedure. To heptane (100 ml) was added phosphorus pentoxide (0.30 g) and 5 mmol of the triorganogermanol. The mixture was stirred for 1 hr at 60°. The liquid was decanted from the solid phosphorus pentoxide and the solvent removed from the solution under vacuum. The residue was recrystallized several times until a constant melting point was obtained. Triphenylgermanium oxide had mp 183–184° (lit.[14] mp 185–187°).

Diphenyl-p-methoxyphenylmethoxygermane.—Diphenyl-p-methoxyphenylbromogermane (1.0 g, 2.5 mmol) was dissolved in an ether solution (100 ml) containing anhydrous methanol (1.0 ml). Anhydrous ammonia gas was bubbled under the surface of the solution for 2 min. The solution was filtered and the solvent removed from the filtrate under reduced pressure leaving a clear liquid (0.88 g, 99% yield) which was the desired product. Since the methoxide is very sensitive to moisture it must be stored in a desiccator. The pmr spectrum consisted of three absorption peaks—a multiplet in the aromatic region at −6.93–7.35 ppm, a singlet at −3.70 ppm due to the methoxy portions on the aromatic rings, and a singlet at −3.62 ppm due to the methoxy protons attached to germanium—in the expected ratio of 14:3:3.

Preparation of a Hydroperoxide. Method I.—Triphenylbromogermane (2.0 g, 5.2 mmol) was dissolved in anhydrous ether (200 ml) to which 98% hydrogen peroxide (2.0 ml, 85 mmol) had been added. The solution was stirred for several minutes at 0° and then anhydrous ammonia was bubbled under the surface for 30 sec, precipitating ammonium bromide. The reaction was quenched with distilled water (30 ml). The organic phase was washed twice with 30-ml portions of water and dried over magnesium sulfate for 10 min. The solution was filtered and the filtrate evaporated under vacuum in a rotary evaporator to give white crystalline triphenylgermyl hydroperoxide (1.1 g, 55% yield). After two recrystallizations from diethyl ether, crystals which melted at 137.5–138° were obtained.

Method IIa.—Diphenyl-p-methoxyphenylmethoxygermane (2.0 g, 5.5 mmol) was placed in a glass tube closed at one end, together with anhydrous ether (20 ml) and a small magnetic stirring bar. To the solution was added 98% hydrogen peroxide

(12) C. A. Kraus and L. S. Foster, *J. Amer. Chem. Soc.*, **49**, 457 (1927).
(13) O. H. Johnson and W. H. Nebergall, *ibid.*, **71**, 1720 (1949).
(14) A. G. Brovic, *ibid.*, **77**, 5059 (1955).

(2.0 ml, 85 mmol). The mixture was stirred rapidly and a stream of dry nitrogen was allowed to pass over the top of the open tube until most of the ether had evaporated. The tube was then connected to a vacuum line and the pressure was slowly reduced to 0.20 mm for 4 hr. There remained at the end of this treatment 2.0 g (99% yield) of a clear viscous oil, which was diphenyl-*p*-methoxyphenylgermyl hydroperoxide.

Preparation of a Bisgermyl Peroxide. Method IIb.—Diphenyl-*p*-trifluoromethylphenylchlorogermane (2.0 g, 4.8 mmol) was dissolved in a solution of anhydrous ether (200 ml) and hydrogen peroxide (0.289 g, 8.5 mmol). At 25° anhydrous ammonia gas was bubbled under the surface for 2 min, and the mixture stirred for another 5 min. The mixture was then filtered through a medium fritted-glass filter and the solvent removed from the filtrate. There remained a clear viscous oil (6.65 g) which was dissolved in 10 ml of pentane and cooled to −20°. The white precipitate which formed (3.70 g, 57% yield), after collection by filtration, had an active oxygen content 2.07%. After two recrystallizations from pentane a material having mp 134–137° was obtained.

The Thermal Decomposition of Organogermanium Peroxides and Hydroperoxides[1]

RALPH L. DANNLEY AND GEORGE C. FARRANT

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

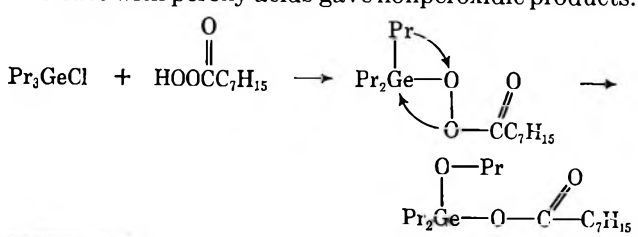
Received July 8, 1968

The thermal decomposition reactions of a number of organogermanium peroxides and hydroperoxides were studied to gain information about the mechanism of the cleavage of the peroxidic link when bound to germanium. Bis(triphenylgermyl) peroxide thermally decomposed with first-order kinetics (E_a = 33.7 kcal/mol) in hexadecane in the absence of oxygen at 190–210° yielded phenol, diphenylgermanium oxide, triphenylgermanol, but no oxygen. The migratory aptitudes of the phenyl and the *p*-trifluoromethylphenyl groups in the decomposition of bis(diphenyl-*p*-trifluoromethylphenylgermyl) peroxide were about equal, consistent with a free-radical mechanism. The thermal decomposition of triphenylgermyl hydroperoxide (1.0 mmol) in *o*-dichlorobenzene produced oxygen (0.17 mmol), water (0.35 mmol), and triphenylgermanol (0.93 mmol) as the major products, and phenol (0.06 mmol) and diphenylgermanium oxide (0.07 mmol) as the minor products. The effect of solvents, radical initiators, radical inhibitors, and ultraviolet light were consistent with a radical mechanism producing these products. The products of the thermal decomposition of triphenylgermyl hydroperoxides in which one of the phenyl groups was substituted in the *para* position gave a migratory aptitude series (p-$CH_3OC_6H_4$, 1.98; p-CF_3-C_6H_4, 1.36; C_6H_5, 1.00) consistent with a radical mechanism for the formation of phenols in this reaction. Triphenylgermyl hydroperoxide decomposed in *o*-dichlorobenzene at 150–170° in an initially oxygen-free system with zero-order kinetics at 0.01 *M* concentration (E_a = 35 kcal/mol) but followed no simple order at higher concentrations. The thermal decomposition of tricyclohexylgermyl hydroperoxide (1.0 mmol) produced cyclohexene (0.56 mmol), cyclohexanol (0.06 mmol), tricyclohexylgermanol (0.29 mmol), and dicyclohexylgermanium oxide (0.18 mmol).

Although there have been several reports[2-4] of the synthesis of organogermanium peroxides, and a disclosure of the synthesis of organogermanium hydroperoxides,[5,6] relatively little is known about the stabilities of these substances or their decomposition products which would permit comparison with the analogous compounds of the other group IVb elements.

Davies[4] suggested a nucleophilic migration of the phenyl group to oxygen to explain his finding that 1-methyl-1-phenylethyl hydroperoxide and germanium tetrachloride gave rise in the course of a few days to phenol and other nonperoxidic products. However, the initial germanium peroxide was not isolated. Davies

also suggested a 1,2 rearrangement to explain his observation that the treatment of alkylgermanium chlorides with peroxy acids gave nonperoxidic products.[4]



Both Davies[4] and Rieche[3] and their coworkers postulated that germanium peroxides undergo some homolytic scission of the peroxide bond because the compounds catalyzed the polymerization of vinyl monomers. However, the extent of the radical *vs.* ionic processes in the decomposition of these compounds has not been established.

It was the purpose of the present investigation to determine whether the symmetrical peroxides and the hydroperoxides of germanium undergo homolysis or heterolysis of the peroxidic link and to determine the kinetics and products of the thermal decomposition.

Results and Discussion

Thermal Decomposition of Bis(triarylgermyl) Peroxides.—The thermal decomposition of bis(triphenylgermyl) peroxide in hexadecane or *o*-dichlorobenzene occurs *via* a first-order process with an activation energy of 33.7 ± 1.5 kcal/mol[7] (Table I). The products of

(1) (a) Supported by the U.S. Army Research Office (Durham) through Grant No. DA-ARO(D)-31-124-G720. (b) Taken in part from the dissertation of G. C. Farrant submitted in Jan. 1968 to the Graduate School of Case Western Reserve University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (c) Presented in part at the first Central Regional Meeting of the American Chemical Society, Akron, Ohio, May 10, 1968.

(2) A. Rieche and J. Dahlmann, *Angew. Chem.*, **71**, 169 (1959).
(3) A. Rieche and J. Dahlmann, *Ann.*, **676**, 19 (1964).
(4) A. G. Davies and C. D. Hall, *J. Chem. Soc.*, 3835 (1959).
(5) R. L. Dannley and G. Farrant, *J. Amer. Chem. Soc.*, **88**, 637 (1966).
(6) R. L. Dannley and G. Farrant, *J. Org. Chem.*, **34**, 2428 (1969).
(7) A referee has pointed out that the calculated value of log *A* is *ca.* 12, which is considerably lower than the corresponding values of 15–16 [(a) R. Hiatt and K. C. Irwin, *J. Org. Chem.*, **33**, 1436 (1968)] for many carbon peroxide decomposition. However, peroxides of elements other than carbon do yield similar low values for their first-order thermal decompositions. Thus log *A* is 10.1–10.8 for silicon hydroperoxides [(b) R. L. Dannley and G. Jalics, *ibid.*, **30**, 3848 (1965)], 11.4 for bisdiphenylphosphinic peroxide [(c) R. L. Dannley and K. R. Kabre, *J. Amer. Chem. Soc.*, **87**, 4805 (1965)], and 12.2 for trimethyltin hydroperoxide in dilute solution [(d) R. L. Dannley and W. A. Aue, *ibid.*, **30**, 3845 (1965)]. The mechanisms of all these reactions are not clearly established but they are first order with respect to peroxide and there is some evidence for free-radical intermediates.

TABLE I
KINETIC DATA FOR THE THERMAL DECOMPOSITION OF BIS(TRIPHENYLGERMYL) PEROXIDE (0.01 *M*)

Solvent	Temp., °C	$k \times 10^5$, sec^{-1}	Half-life, min
Hexadecane[a]	210	34.5	34
	210	34.0	35
	200	15.9	73
	190	7.40	156
	190	7.20	159
	178.5	5.15	365
	150	0.252[b]	4570[b]
o-Dichlorobenzene	150	0.242	4750
	150	0.231	5020

[a] $E_a = 33.7 \times 1.5$ kcal/mol. [b] Extrapolated from the plot of $\log k$ *vs.* $1/T$.

decomposition of the peroxide in *o*-dichlorobenzene solution were determined. No oxygen was evolved when the reaction was run in a closed system with an initially oxygen-free system. The initial germanium-containing products were not directly identified; instead the mixture of decomposition products was treated with anhydrous hydrogen chloride to convert them into the volatile chlorides which were analyzed by glpc.

$$\underset{1.0}{(C_6H_5)_3GeOOGe(C_6H_5)_3} \xrightarrow{\Delta} \underset{}{(\quad)} \xrightarrow{HCl} \underset{0.27}{C_6H_5OH} + \underset{0.43}{(C_6H_5)_2GeCl_2} + \underset{1.44}{(C_6H_5)_3GeCl}$$

The acid treatment was particularly necessary for the analysis of the diphenylgermanium moieties, since these germanium oxides exist in several modifications which are difficult to separate. It is apparent from the product analysis that the reaction proceeds by two pathways, one yielding phenol and diphenylgermanium moieties, the second giving triphenylgermanol or one of its derivatives. It has been shown that the analytical procedure does not cleave the carbon–germanium bond in this system. Therefore the diphenylgermanium moieties are accurately measured and the corresponding phenol yield is low, probably owing to partial oxidation by unreacted peroxide during the course of the reaction.

The thermal decomposition of bis(diphenyl-*p*-trifluoromethylphenylgermyl) peroxide in *o*-dichlorobenzene showed that the migratory aptitudes of the trifluoromethylphenyl and phenyl groups are roughly

$$\underset{1.0}{[CF_3C_6H_4(C_6H_5)_2GeO]_2} \xrightarrow{160^\circ\ HCl} \begin{matrix} \underset{0.089}{CF_3C_6H_4OH} + \underset{0.13}{(C_6H_5)_2GeCl_2} \\ \underset{0.14}{C_6H_5OH} + \underset{0.34}{CF_3C_6H_4C_6H_5GeCl_2} \\ \underset{1.44}{CF_3C_6H_4(C_6H_5)_2GeCl} \end{matrix}$$

equal ($CF_3C_6H_4/C_6H_5 = 1.25$ from the phenol analysis and 0.75 from the germanium chloride analysis). Migratory aptitudes for free-radical migrations have not been well established but a nitrophenyl/phenyl ratio of 4.0–4.4:1 was obtained for both the homolytic decomposition of diphenyl-*p*-nitrophenylmethyl hydroperoxide[8] and the oxidation of diphenyl-*p*-nitrophenylcarbinol with lead tetraacetate.[9,10] The nitro group is expected to give greater resonance stabilization than a trifluoromethyl group. Therefore the migratory aptitude here observed is consistent with a homolytic process but not with an ionic rearrangement to a positively charged site, for which it would be expected that the phenyl group would migrate in preference to the trifluoromethylphenyl group by several orders of magnitude.

A possible mechanism for the reaction involves the homolysis of the peroxide bond and rearrangement of the resultant radical. The rearrangement must be fairly slow since the major product of the reaction is a

$$Ar_3GeOOGeAr_3 \longrightarrow 2Ar_3GeO\cdot$$
$$Ar_3GeO \longrightarrow Ar_2ArOGe\cdot$$
$$Ar_2ArOGe\cdot + Ar_3GeO \longrightarrow Ar_2ArOGeOGeAr_3$$

triphenylgermyl moiety. The lack of any coupled product containing a germanium to germanium bond is in marked contrast to the decomposition of trityl peroxide in which the main product isolated was 1,1,2,2-tetraphenyl-1,2-diphenoxyethane.[11] This result indicates that the rearranged triphenylgermyloxy radicals do not accumulate in concentrations high enough to produce coupled products, and that these radicals are not stabilized by delocalization of the unpaired electron to the same degree that the corresponding carbon radicals are.

$$\begin{matrix} (C_6H_5)_2C{-}C(C_6H_5)_2 \\ \quad | \qquad\quad | \\ C_6H_5O \quad OC_6H_5 \end{matrix}$$

Thermal Decomposition of Triarylgermyl Hydroperoxides.—The products of the thermal decomposition of triphenylgermyl hydroperoxide under a variety of conditions are shown in Table II. Although these quantitative results were obtained by glpc after hydrogen chloride treatment of the reaction mixture, in preliminary experiments both phenol and triphenylgermanium oxide were isolated in pure form. The oxide probably arose from condensation of two molecules of the germanol, since triphenylgermanol undergoes this reaction under the conditions used for the decomposition of the hydroperoxide.

$$2(C_6H_5)_3GeOH \longrightarrow (C_6H_5)_3GeOGe(C_6H_5)_3 + H_2O$$

Although a 95% recovery of the germanium was usually obtained, only 34% of the original oxygen content of the peroxide was accounted for in the identified products. The reaction mixtures were dark, probably owing to unidentified oxidation products which are responsible for the poor oxygen balance.

The products identified indicate that two competing reactions occurred. The hydroperoxide primarily underwent reduction but some (5–10%) rearrangement also was observed. The principle reaction, forming oxygen and a triphenylgermyl moiety, must be free radical in nature for the product ratios (Table II) were not appreciably affected by a major change in the polarity of the solvent, the oxygen yield is increased by addition of a radical initiator and decreased by a radical inhibitor, and the decomposition is accelerated by ultraviolet light. In addition, the small by-product

(8) P. D. Bartlett and J. Cotman, *J. Amer. Chem. Soc.*, **72**, 3095 (1950).

(9) W. H. Starnes Jr., *ibid.*, **89**, 3368 (1967).
(10) W. H. Starnes Jr., *ibid.*, **90**, 5807 (1968).
(11) H. Wieland, *Ber.*, **44**, 2553 (1911).

TABLE II
PRODUCTS OF THE DECOMPOSITION OF TRIPHENYLGERYML HYDROPEROXIDE (1.0 mol)

Solvent	Added conditions	$(C_6H_5)_3$-GeOOH concn, *M*	Temp, °C	Amt, mol			
				O_2	$(C_6H_5)_3GeCl$	$(C_6H_5)_2GeCl_2$	C_6H_5OH
o-$C_6H_4Cl_2$[a,b]	None	0.05	160	0.13 ± 0.05	0.93 ± 0.02	0.06 ± 0.02	0.07 ± 0.02
$C_6H_5NO_2$[a,c]	None	0.05	160	0.17 ± 0.03	0.90 ± 0.02	0.05 ± 0.01	0.01 ± 0.01
o-$C_6H_4Cl_2$[d]	ABIN[e]	0.05	120	0.33	0.95	0.04	0.06
$CH_3CO_2C_2H_5$[d]	Uv light	0.005	77	*f*	0.93	0.05	0.06
o-$C_6H_4Cl_2$[d]	DPPH[g]	0.95	150	0.08	0.99	<0.005	<0.005

[a] Three separate decomposition solutions were analyzed, and the results averaged. [b] Water (0.34) yield was determined in only one run. [c] Nitrophenols were also obtained: *o*, 0.0022; *m*, 0.0027; *p*, 0.0074. [d] Only one decomposition solution analyzed. [e] Azobisisobutyronitrile concentration 0.005 *M*. [f] Not determined. [g] 2,2-Diphenyl-1-picrylhydrazyl concentration 0.005 *M*.

yields of nitrophenols obtained when nitrobenzene is used as a solvent correspond in isomer distribution (*ortho* 18%, *meta* 22%, *para* 60%) to the values reported for the hydroxylation of this substrate with Fenton's reagent[12] (*ortho* 25–30%, *meta* 20–25%, *para* 50–55%).

The data in Table II also support a free-radical mechanism for the rearrangement process. Thus the amount of rearrangement is unaffected by the polarity of the solvent, ultraviolet light, or the presence of a radical initiator. Confirmation of the homolytic classification was obtained from the relative migratory aptitudes observed in the thermal decomposition of substituted triphenylgermyl hydroperoxides (Table III).

TABLE III
PRODUCTS FOR THE THERMAL DECOMPOSITION OF *para*-SUBSTITUTED TRIPHENYLGERMYL HYDROPEROXIDES (1 mol)
[*p*-$XC_6H_4(C_6H_5)_2GeOOH$][c]

Product	Amt, mol	
	X = CF_3[a]	X = CH_3O[b]
O_2	0.18 ± 0.060	0.12 ± 0.03
C_6H_5OH	0.038 ± 0.010	0.034 ± 0.005
XC_6H_4OH	0.025 ± 0.010	0.035 ± p.005
$(C_6H_5)_2GeCl_2$	0.033 ± 0.010	0.33 ± 0.12[c]
$XC_6H_4C_6H_5GeCl_2$	0.046 ± 0.010	0.051 ± 0.002[c]
$XC_6H_4(C_6H_5)_2GeCl$	0.88 ± 0.030	0.61 ± 0.010[c]

[a] Results are the average analyses of three separate runs. [b] Results are the average analyses of two separate runs. [c] Hydrogen chloride treatment cleaved some of the anisyl groups from the germanium products. Therefore the diphenyldichlorogermane analysis is too high, and the methoxyphenylgermanium chlorides too low. [c] Registry no.: X = CF_3, 19987-82-7; X = CH_3O, 19987-83-8.

From the yields of phenols, the migratory aptitudes are, for *p*-anisyl, 1.9 ± 0.1; *p*-trifluoromethylphenyl, 1.3 ± 0.4; and phenyl, 1.0. With diphenyl-*p*-trifluoromethylphenylgermyl hydroperoxide, the diarylgermyl dichloride analysis could be used to confirm the migratory aptitude (1.4 ± 0.2), but a similar check could not be obtained with diphenyl-*p*-methoxyphenylgermyl hydroperoxide, since some of the anisyl groups are cleaved from the germanium-containing products by the hydrogen chloride treatment.[6]

The low migratory aptitudes obtained for substituted phenyl groups with widely different electronic requirements are characteristic of a homolytic rearrangement process. The anisyl–phenyl ratio slightly greater than 1 is comparable with the values of 1.1–3.5 for anisyl migrations in the free-radical oxidation of diphenyl-*p*-methoxyphenylcarbinol with lead tetraacetate[9,10] and the values of 0.35–1.2 reported for anisyl migrations in carbon radicals.[13–15] In contrast, in ionic reactions such as the acid-catalyzed decomposition of diphenyl-*p*-methoxyphenylmethyl hydroperoxide[16] or the rearrangement of the corresponding perbenzoate,[17] exclusive anisyl migration occurs.

The observations above are consistent with the mechanism given in eq 1–5. The reaction is initiated

$$Ar_3GeOOH \longrightarrow Ar_3GeO\cdot + \cdot OH \quad (1)$$

$$Ar_3GeOOH + R\cdot \longrightarrow RH + Ar_3GeOO\cdot \quad (2)$$

$$2Ar_3GeOO\cdot \longrightarrow 2Ar_3GeO\cdot + O_2 \quad (3)$$

$$Ar_3GeO\cdot \longrightarrow Ar_2\dot{G}eOAr \quad (4)$$

$$Ar_2\dot{G}eOAr + Ar_3GeO\cdot \longrightarrow Ar_2ArOGeOGeAr_3 \quad (5)$$

(eq 1) thermally or photolytically by dissociation into the triarylgermyloxy and hydroxy radicals. Oxygen is produced through an induced decomposition (eq 2) by any of the radicals generated to give the triarylgermylperoxy radical which, from its analogy to alkylperoxy radicals,[18–22] should yield oxygen and triarylgermyloxy radicals (eq 3) or bis(triarylgermyl)peroxide. The bisperoxide cannot be an important intermediate in any proposed mechanism since triphenylgermyl peroxide decomposes some 14 times slower than triphenylgermyl hydroperoxide in *o*-dichlorobenzene. However, the peroxide formation in low yields cannot be discounted at this time.

The rearrangement (eq 4) must be slow relative to the other reactions of the triarylgermyloxy radicals for only 5–10% of this reaction occurs. It cannot be a cage process because it is eliminated by the addition of small quantities (10%) of 2,2-diphenyl-1-picrylhydrazyl. Although the original product of rearrangement was not isolated, it may have the structure depicted in eq 5 for such a compound is stable in the silicon series.[23]

Kinetics of the Thermal Decomposition of Triphenylgermyl Hydroperoxide.—Reproducible kinetic data for the thermal decomposition of triphenylgermyl hydroperoxide were difficult to obtain. However, by using carefully purified material (mp 137.5–139°) the reproducible values given in Table IV were obtained.

(12) H. H. Loebel, G. Stein, and J. Weiss, *J. Chem. Soc.*, 2079 (1949).

(13) C. Rüchart, *Ber.*, **94**, 2609 (1961).
(14) C. Rüchart and H. Trautwein, *ibid.*, **96**, 160 (1963).
(15) C. Rüchart and J. C. Hect, *ibid.*, **98**, 2471 (1965).
(16) W. Dilthey, F. Quint, and H. Dierichs, *J. Prakt. Chem.*, **151**, 25 (1938).
(17) I. J. Levine, Ph.D. Dissertation, University of Kansas, 1960, *Dissertation Abstr.*, **21**, 2478 (1961).
(18) G. A. Russell, *J. Amer. Chem. Soc.*, **79**, 3871 (1957).
(19) P. D. Bartlett and T. G. Traylor, *ibid.*, **85**, 240 (1963).
(20) H. S. Blanchard, *ibid.*, **81**, 4548 (1959).
(21) J. R. Thomas, *ibid.*, **87**, 3935 (1965).
(22) P. D. Bartlett and G. Guaraloi, *ibid.*, **89**, 4799 (1967).
(23) G. Jalics, Ph.D. Dissertation, Western Reserve University, 1964.

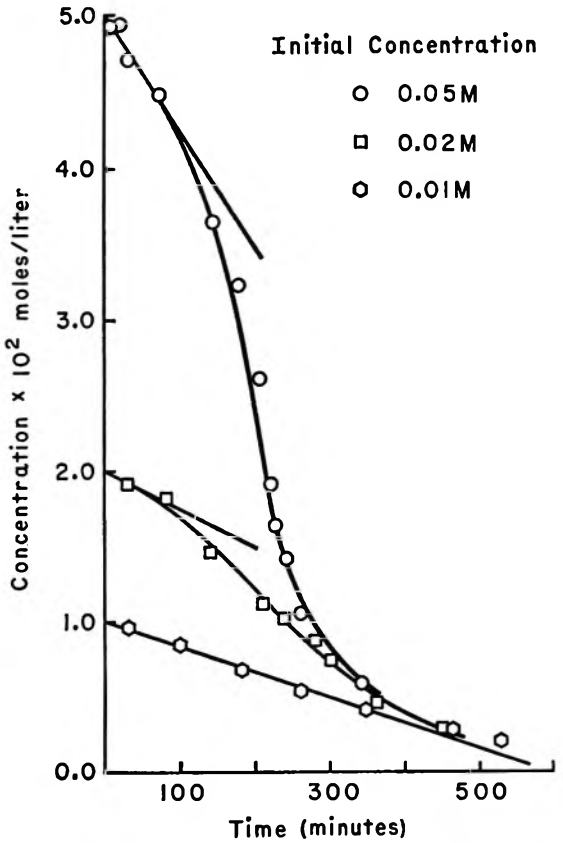


Figure 1.—Plot of concentration *vs.* time for the thermal decomposition of triphenylgermyl hydroperoxide in *o*-dichlorobenzene at 160.0°.

TABLE IV
KINETIC DATA FOR THE DECOMPOSITION OF TRIPHENYLGERMYL HYDROPEROXIDE IN *o*-DICHLOROBENZENE

Temp, °C	Concn, *M*	$K_0 \times 10^7$, mol/sec	Half-life, min	Remarks
170[a]	0.01	7.0	111	
170[a]	0.01	6.9	120	
160[a]	0.01	2.88	290	
160[a]	0.01	2.83	295	
150[a]	0.01	1.11	750	
150[a]	0.01	1.07	770	
150	0.05	5.0	317	Initial rate
150	0.01	1.2	650	Run in Teflon bottle
150	0.01	1.29	600	Glass wool added
160	0.02	5.5	240	Initial rate
160	0.05	13.9	210	Initial rate
160	0.01	1.67	490	0.1 mmol of $(C_6H_5)_3GeOH$ added
160	0.01	2.80	297	Reaction carried out under air atmosphere

[a] These values were used to calculate the E_a (3.50 ± 0.3 kcal/mol).

The hydroperoxide decomposed in *o*-dichlorobenzene in a very complex manner (not a simple first-order process as originally reported[5]) dependent upon the initial hydroperoxide concentration (Figure 1). At concentrations of 0.01 *M* or less, a zero-order plot was obtained with an activation energy of 35.5 ± 1.0 kcal/mol (Figure 2). At higher concentrations the order changed over the course of the reaction. However the initial portion (5–10%) of the reaction followed first-order kinetics, since the plot of the log of the initial rate *vs.* log of the initial concentration gives a straight line with slope +1.06 (Figure 3). The initial first-order rate

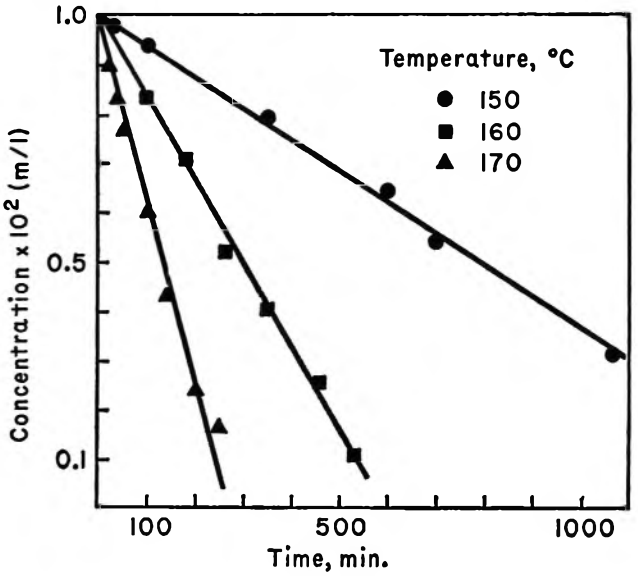


Figure 2.—Plot of concentration *vs.* time for the thermal decomposition of triphenylgermyl hydroperoxide in *o*-dichlorobenzene: initial concentration, 0.01 *M*.

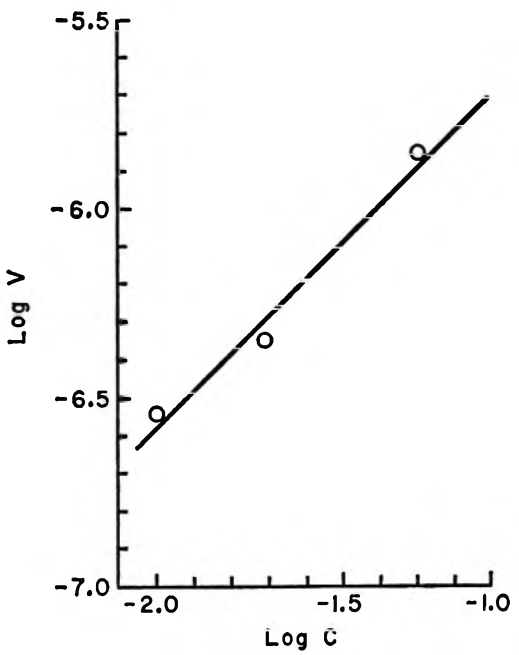


Figure 3.—Plot of log initial rate (V) of hydroperoxide disappearance at 160° *vs.* log initial concentration (C) for the thermal decomposition of triphenylgermyl hydroperoxide in *o*-dichlorobenzene.

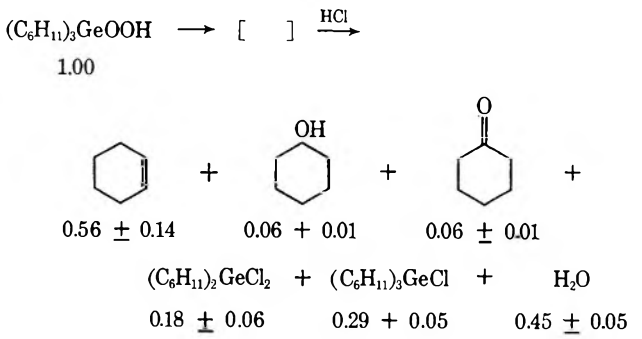
and the succeeding complex order are consistent with the initial homolysis of the peroxide link followed by induced decomposition, as proposed.

The cause of the pseudo-zero-order reaction, however, is not clear. While some zero-order reactions are due to surface reactions it was shown that altering the surface of the vessel by adding glass wool or changing to a Teflon vessel neither appreciably affected the rate nor changed the order. The rate of the reaction was also unaffected by either air or a nitrogen atmosphere (Table IV), but it was found that the addition of 0.1 *M* triphenylgermanol to the system decreased the rate appreciably (49%). The solvents and the peroxide are of the highest purity obtainable but the presence of

trace amounts of impurities which might cause the zero-order rate cannot be discounted.

The germanium compound decomposed at a much slower rate (half-life at 150°, 325 *vs.* 25 min) and with a higher activation energy (35.5 *vs.* 27.0 kcal/mol) than the corresponding silicon compound.[7b] Although this result is surprising, it is in accord with Rieche's[3] qualitative observation that bis(triphenylgermyl) peroxide is more stable than the corresponding bis(triphenylsilicon) peroxide.

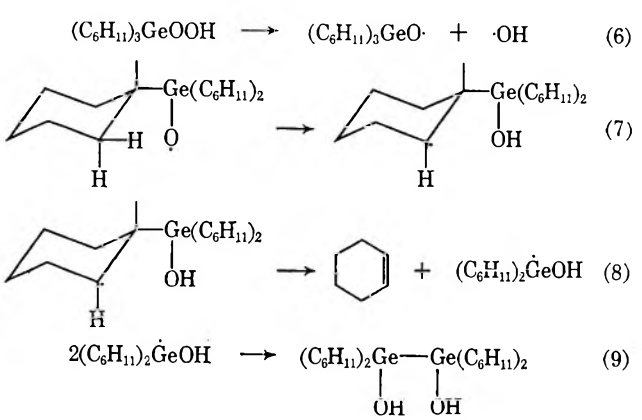
Thermal Decomposition of Tricyclohexylgermyl Hydroperoxide.—The products of the thermal decomposition of tricyclohexylgermyl hydroperoxide in *o*-dichlorobenzene differed widely in nature from the products obtained from the triaryl anologs. As no oxygen was evolved, an induced decomposition yielding a peroxy



radical must be excluded. The low recovery of germanium moieties (47%) indicates that some products containing germanium to germanium bonds may have been formed, for such compounds are not converted into volatile halides by the hydrogen chloride treatment. The yield of cyclohexene (56%) is similar to the quantity of germanium moiety unaccounted for (53%), although this may be fortuitous.

The cyclohexanol, by analogy to the triphenylgermyl hydroperoxide decomposition, should arise from a rearrangement. However, the identical yields of cyclohexanol (6%) and cyclohexanone (6%) suggest a disproportionation by cyclohexyloxy radicals. Also, the combined yield of these two compounds (12%) is too high compared with the maximum phenyl rearrangement yield (7%) for a radical rearrangement. Therefore, these data are insufficient to select between alternate mechanisms.

The homolytic mechanism given by eq 6–9 is proposed to account for the formation of cyclohexene and the low recovery of organochlorogermanes. In the carbon system (homolytic addition of an alcohol to an olefin) the equilibrium of eq 8 lies to the left but a germanium–carbon bond is so much weaker (32 kcal $Ge-C_6H_5$)[24] than a carbon–carbon bond (90 kcal for $C-C_6H_5$)[25] that eq 8 as written should be energetically favored.



Experimental Section

Triphenylchlorogermane, triphenylbromogermane, diphenyldichlorogermane, tricyclohexylchlorogermane, and germanium tetrachloride were purchased either from Metallomer Laboratories or Alfa Inorganics, and were used without further purification. The germanium peroxides and hydroperoxides as well as the reference organogermanium chlorides, hydroxides, and oxides were prepared according to methods outlined in a previous paper.[6]

Dicyclohexyldichlorogermane ($n^{25}D$ 1.5257) was prepared by adding cyclohexylmagnesium chloride (60 mmol) in ether (250 ml) to an ice-cold solution of germanium tetrachloride in toluene (650 ml) over a period of 2 hr. The mixture was then warmed to room temperature, filtered, and the solvent removed from the filtrate. The residue was distilled at reduced pressure, and the fraction (2.0 g, 21% yield) boiling between 117 and 120° (0.15 mm) was shown to be better than 99% pure by glpc (column D). *Anal.* Calcd for $C_{12}H_{22}GeCl_2$: C, 46.51; H, 7.16; Ge, 23.47. Found: C, 46.61; H, 7.27; Ge, 23.70.

Analytical Procedures.—All glpc analyses were carried out on an Aerograph (Varian Associates) gas chromatograph, Model 1520B, using a thermal conductivity detector. The temperature of the injection port and detector were maintained at 250–270°. The chromatographic columns and conditions used are given in Table V.

The composition of a reaction solution was quantitatively determined using the internal standard technique. Calibration fractors were obtained from standard solutions of the reference chlorides and an appropriate internal standard. Three to five determinations of both the reaction mixture and the standard solution were made for each analysis and the results averaged. Usually the precision was within ±3–5% between any two runs.

Product Analysis of the Thermal Decomposition of the Hydroperoxides and Peroxides.—The hydroperoxide or peroxide (1.00 mmol) and 20.0 ml of the purified solvent were placed in a 25-ml volumetric flask connected to a manifold containing three valves. One valve was attached by means of tygon tubing to a gas buret filled with mercury, another was connected to a tank of dry nitrogen (G.E. Lamp grade), while the third valve could be vented to the atmosphere. The system was purged with nitrogen for 1 hr and the system closed. It was determined from other experiments that the atmosphere contained better than 99.9% nitrogen. The solution was then heated to 150–160° from 12 to 72 hr, depending upon the compound, then cooled to room temperature. After the system came to equilibrium, the pressure, temperature, and volume of gas increase were measured.

To prove that the evolved gas was oxygen, the atmosphere was assayed by withdrawing 0.50–2.0-ml samples *via* a gas-tight syringe and analyzing them on the gas chromatograph (column B). The concentration of oxygen was determined by multiplying the ratio of the area of the oxygen to nitrogen peaks times the volume above the solution. In all instances in which an air-tight syringe was used, good agreement between the concentration of oxygen calculated from the gas increase and that analyzed by glpc was obtained, indicating that the only gaseous product of the reaction was oxygen.

The solution was then assayed for active oxygen, and in all instances better than 99% of the hydroperoxide or peroxide had decomposed. A portion of the solution (5.0 ml) was withdrawn and *m*-chlorophenol added as an internal standard. The solution was treated with anhydrous hydrogen chloride for 5 min and then analyzed for phenols (columns A or E). In some instances the trimethylsilyl derivatives of the phenols were prepared by treating an aliquot (5.0 ml) of the decomposition solution with 5.0 ml of hexamethyldisilazane. A pinch of sand was added together with the internal standard (*m*-dinitrobenzene) and the mixture refluxed for 3 hr. It was shown independently that the procedure quantitatively formed the trimethylsilyl ethers from the phenols present in the reaction mixture. The trimethylsilyl ethers were analyzed

(24) K. H. Birr, *Z. Anorg. Allg. Chem.*, **316**, 175 (1962).
(25) J. S. Roberts and H. A. Skinner, *Trans. Faraday Soc.*, **45**, 339 (1949).

TABLE V
CHROMATOGRAPHIC COLUMNS AND CONDITIONS

Column	Size ft × in.	Material	Packing	Conditions: Temp, °C	Conditions: He flow rate, ml/min
A	8 × 0.25	Copper	10% Carbowax 20M on Chromosorb W	180–210	30–60
B	8 × 0.25	Copper	Molecular Sieve 5A	50	60
C	8 × 0.25	Copper	5% Silicone oil D.C. 710 on Chromosorb G; A/W, DMCS treated, 80–100 mesh	220–230	150–200
D	5 × 0.25	Stainless steel	5% Silicone oil D.C. 710 on Chromosorb; A/W, DMCS treated, 80–100 mesh	220–255	150–300
E	5 × 0.25	Stainless steel	5% FFAP on Chromosorb G; A/W, DMCS treated, 80–100 mesh	195–210	30
F	25 × 0.25	Copper	5% silicone gum rubber on Chromosorb G; A/W, DMCS treated, 80–100 mesh	125	60
G	6 × 0.25	Copper	10% butadiol adipate on Anakrom 70–80 mesh	100	120
H	5 × 0.125	Stainless steel	Poropak Q, 150–170 mesh	100	30
I	10 × 0.25	Stainless steel	5% STAP on Chromsorb W; A/W, DMCS treated, 80–100 mesh	125	100

on columns F and I. Another 5.0-ml aliquot of the decomposition solution was withdrawn, triphenylmethane added as an internal standard, and the mixture treated with hydrogen chloride for 10 min. The resulting solution was then analyzed for organogermanium chlorides (column C or D). Water was determined by adding ethanol as an internal standard to another 5.0-ml portion of the decomposition mixture and analyzing on column H. When tricyclohexylgermyl hydroperoxide was used, cyclohexene, cyclohexanol, and cyclohexanone were analyzed on columns F and G using *p*-xylene as the internal standard.

Isolation of Organogermanium Compounds.—The germanium-containing compounds resulting from the thermal decomposition of the hydroperoxides were isolated by removing the solvent under vacuum and then purified by chromatography through neutral alumina. The eluents were evaporated and the solid residues, recrystallized from appropriate solvents, agreed in physical properties (melting point, ir and nmr spectra) with authentic materials described in a preceding paper.[6] The yields are given in Table VI.

TABLE VI
YIELDS OF GERMANIUM COMPOUNDS ISOLATED FROM THE THERMAL DECOMPOSITION OF ORGANOGERMYL HYDROPEROXIDES

Hydroperoxide	Organogermanium product	Yield[a]
$(C_6H_5)_3GeOOH$	$[(C_6H_5)_3Ge]_2O$	0.30
$CF_3C_6H_4(C_6H_5)_2GeOOH$	$[CF_3C_6H_4(C_6H_5)_2Ge]_2O$	0.25
$CH_3OC_6H_4(C_6H_5)_2GeOOH$	$[CH_3OC_6H_4(C_6H_5)_2Ge]_2O$	0.29
	$CH_3OC_6H_4(C_6H_5)_2GeOH$	0.18
$(C_6H_{11})_3GeOOH$	$(C_6H_{11})_3GeOH$	0.45

[a] The yields (mole/mole of hydroperoxide) described are not optimum but rather the observed yield after several recrystallizations.

General Kinetics Procedure.—A standard solution of the hydroperoxide or peroxide was prepared. Approximately 50 ml of the solution was placed in a Raysorb-coated (Kimax) 100-ml volumetric flask which had two side arms attached to it. The protective coating prevented any extraneous ultraviolet light below 450 mμ from entering the flask. Through one of the side arms was a glass tube which extended into the flask below the surface of the solution. The other side arm was connected to a trap filled with the solvent to prevent any diffusion of air back into the system. The top of the vessel was sealed with a rubber septum and the system was purged with a stream of nitrogen (approximately 200 cc/min). After 30 min, the nitrogen flow was reduced to 10 cc/min and the flask was placed in a thermostated oil bath (±0.1° at 150° and ±0.2° at 210°). A period of 4 min was allowed for the system to come to equilibrium, after which samples of the solution were periodically withdrawn *via* a needle and syringe and discharged into a hot solution of sodium iodide in 20:80 acetic acid–isopropyl alcohol. This mixture was boiled for 5 min and the liberated iodine back-titrated with a standard solution of sodium thiosulfate. When hexadecane was used as the solvent, the syringe had to be filled with nitrogen to prevent oxidation of the solvents by air at these high temperatures. In all the runs, several determinations of a blank were made; this average value was subtracted from the original titer. In no case did the blank ever exceed 0.3 ml of 0.01 *M* thiosulfate. The zero point titers usually consumed 9–10 ml.

The ultraviolet light catalyzed decomposition of triphenylgermyl hydroperoxide in refluxing ethyl acetate was carried out in a quartz flask by a Rayonet reactor using light at 2537 Å. The temperature was maintained by refluxing (77.1°) the mixture.

Registry No.—Dicyclohexyldichlorogermane, 19978-36-0; bis(triphenylgermyl) peroxide, 5695-57-8: triphenylgermyl hydroperoxide, 5274-38-4.

Permanganate Oxidations. II. Kinetics and Mechanism of the Oxidation of Cyclohexanenitronate and Cyclopentanenitronate Anions[1]

FILLMORE FREEMAN, ARA YERAMYAN, AND FREDERICK YOUNG

Department of Chemistry, California State College, Long Beach, Long Beach, California 90801

Received November 20, 1968

The kinetics of the permanganate oxidation of cyclohexanenitronate (I) and cyclopentanenitronate (II) anions were investigated *via* spectrophotometric stopped-flow techniques from pH 12.5 to 13.5. The reactions were first order in nitronate anions and in permanganate, and zero order in hydroxide ion. A positive salt effect was observed with I, and I was oxidized six times faster than II. $\Delta H^{\ddagger}$ was 7.45 kcal/mol for I and 10.5 kcal/mol for II, and $\Delta S^{\ddagger}$ was −27.8 eu for I and −20 eu for II. The data are consistent with orbital rehybridization in the rate-determiming step which suggests an attack of permanganate at the carbon of the carbon–nitrogen double bond of the nitronate anion.

Very few bimolecular reactions in organic chemistry are characterized by rate constants larger than 1 l. mol^{-1} sec^{-1}. Recently Wiberg and Geer[2] and Freeman and Yeramyan[1] have reported second-order rate constants in excess of 150 l. mol^{-1} sec^{-1} for the permanganate oxidation of alkenes and the anion of phenylnitromethane, respectively. Another rapid reaction of this type is the permanganate oxidation of cycloalkylnitronate anions. Although Schechter and Williams[3-6] have investigated the scope of the permanganate oxidation of nitro compounds to carbonyl compounds, only one report[1] has appeared concerning the kinetics of this extremely rapid reaction. The purpose of the work reported herein was to investigate the kinetics and mechanism of the permanganate oxidation of cyclohexanenitronate (I) and cyclopentanenitronate (II) anions. In this paper we present a detailed kinetic study of I and II.

Experimental Section

Reagents.—Distilled water was purified by passing through an ion-exchange cartridge (Type R-2, Illinois Water Treatment Co., Rockford, Ill.).

Mallinckrodt reagent grade sodium chloride was used without further purification to adjust ionic strength. Acculute standard volumetric potassium hydroxide (CO_2 free) concentrate was diluted to the specified volume for the desired pH. The pH of the solutions were taken as those measured potentiometrically. Potassium permanganate stock solutions, 2.00×10^{-2} M, were prepared from Acculute standard volumetric solutions. The stock solution was stored under nitrogen and was standardized when not used frequently. (The absorbancy index was checked for permanganate before each set of kinetic runs.) These stock solutions did not deteriorate for 5–6 months when kept in the dark. Deionized water was used to prepare standard stock solutions.

Nitrocyclohexane (III) (Aldrich) was distilled at reduced pressure immediately before use. Nitrocyclopentane (IV) was prepared according to the procedure of Kornblum and Powers:[7] bp 62–63° (8 mm); $n^{20}D$ 1.4531 [lit.[7] bp 48° (1 mm); $n^{20}D$ 1.4539].

Apparatus and Procedures.—Because of the short reaction time, the rates were determined by following spectrophotometrically the disappearance of permanganate in a stopped-flow reactor[8] which permitted study of reactions with half-lives as low as 0.4 sec. A Beckman Model DU instrument was modified with an energy-recording adapter so that the signal output could be followed with a Bristol strip-chart recorder having a 0.20-sec full-scale response and chart speeds up to 120 in./min. The stopped-flow reactor was designed so that the storage and reacting solutions could be well thermostated. A 4- or 10-mm Pyrex cell with a volume of 1.2 or 3 ml was employed. The time required to half fill the cell with the mixed reaction solution was less than 0.2 sec.

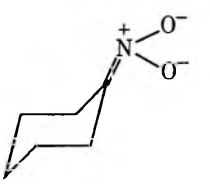
All studies were performed under pseudo-first-order conditions, and the rates were followed until the reactions were 75–90% complete. The rate constants were obtained from plots of $-\ln[\log(T_\infty/T)]$ against time and were calculated on an IBM 360 computer.[9] The rate constants given in the tables are the average of two or more determinations, and the deviations are the *mean* deviations for the set of runs. The small deviations suggest a reasonably good degree of accuracy.

Results

Stoichiometry.—The stoichiometry of the reaction has been verified by Schechter and Williams.[3] Ultravi-

$$3RC{=}NO_2K + 2KMnO_4 + H_2O \longrightarrow 3R_2C{=}O + 2MnO_2 + 3KNO_2 + 2KOH \quad (1)$$

olet spectral determinations with nitrocyclohexane III and nitrocyclopentane IV at pH 13.0 showed that both were almost completely converted into the relatively stable nitronate ions (I and II).[10-13] To ensure that



I

II

permanganate did not enter into subsequent oxidation reactions with the enolic forms of the products or nitrite ion, the rate constants were calculated three times using the data to the first half-life, to the second half-

(1) Previous paper in series: F. Freeman and A. Yeramyan, *Tetrahedron Lett.*, 4783 (1968).

(2) K. B. Wiberg and R. D. Geer, *J. Amer. Chem. Soc.*, **87**, 5202 (1965); **88**, 5827 (1966).

(3) H. Schechter and F. T. Williams, *J. Org. Chem.*, **27**, 3699 (1962).

(4) Although previous workers[3] used a buffered KOH–$MgSO_4$ system, the reactive species presumably is the nitronate anion. Other examples of nonbuffered systems have been reported.[3,5,6]

(5) Additional references for the permanganate oxidation of salts of nitro compounds to carbonyl compounds, in excellent yields, are given in ref 3.

(6) (a) S. S. Nametkin and E. Posdnjakova, *J. Russ. Phys. Chem. Soc.*, **45**, 1420 (1913); (b) S. S. Nametkin and O. Madaeff-Ssitscheff, *Chem. Ber.*, **59**, 370 (1926).

(7) N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957).

(8) Modification of an original design by Professor K. B. Wiberg, Department of Chemistry, Yale University, New Haven, Conn.

(9) We wish to thank the Western Data Computing Center, University of California, Los Angeles, Los Angeles, Calif., for making computer time available to us.

(10) Ultraviolet spectroscopy showed that III and IV were more than 98% converted into I (231 mμ) and II (226 mμ), respectively, under kinetic conditions. See also ref 11.

(11) (a) F. T. Williams, Jr., P. W. K. Flanagan, W. V. Taylor, and H. Schechter, *J. Org. Chem.*, **30**, 2674 (1965). (b) P. W. K. Flanagan, H. W. Amburn, H. W. Stone, J. G. Traynham, and H. Schecter, *J. Amer. Chem. Soc.*, **91**, 2797 (1969).

(12) M. H. Hawthorne, *ibid.*, **79**, 2510 (1957).

(13) A. T. Nielsen, *J. Org. Chem.*, **27**, 2001 (1962).

life, and then to the third half-life. By comparing these values, any deviation from linearity was readily observed. A typical kinetic plot is shown in Figure 1.

Cyclohexanenitronate Anion (I).—The kinetic data for the oxidation of I are summarized in Table I. A plot of k_ψ *vs.* concentration of I gives a straight line that goes through the origin, indicating the rate of oxidation to have a first-order dependence on I. The constancy of the values of k_2 over a tenfold range of hydroxyl ion concentration at constant cyclohexanenitronate anion and permanganate concentrations indicates a zero-order dependence on hydroxide ion. At constant hydroxide ion and cyclohexanenitronate anion concentrations, the rate constants do not alter with changing permanganate concentrations which indicates a first-order dependence on permanganate. These data suggest the following rate law.

$$\frac{-d[MnO_4^-]}{dt} = 2k_2[\text{cyclohexanenitronate anion}][MnO_4^-]$$

TABLE I

RATE DATA FOR THE OXIDATION OF CYCLOHEXANENITRONATE ANION

(μ = 0.5 M, λ 522 mμ, T = 1.0 ± 0.02°, 10-mm cell)

[Nitrocyclohexane] × 10^4 M	[OH$^-$], M	[MnO$_4^-$] × 10^4 M	$2k_\psi$[a] × 10^2 sec^{-1}	$2k_2$, M^{-1} sec^{-1}
15.0	0.10	4.00	51 ± 1	337
20.0	0.10	4.00	66 ± 1	330
25.0	0.10	4.00	83 ± 1	330
30.0	0.10	4.00	103 ± 4	345
40.0	0.10	4.00	137 ± 1	342
45.0	0.10	4.00	148 ± 2	328
55.0	0.10	4.00	176 ± 2	321
40.0	0.032	4.00	112 ± 4	279
40.0	0.05	4.00	117 ± 2	293
40.0[b]	0.08	4.00	116	291
40.0	0.32	4.00	117 ± 3	292
40.0[c]	0.10	6.00	121 ± 3	301
40.0[c]	0.10	8.00	119 ± 1	297
40.0[c]	0.10	10.00	120 ± 1	301
40.0[c]	0.10	12.00	117 ± 1	291
40.0[c]	0.10	14.00	120 ± 3	301

[a] Pseudo-first-order rate constant with mean deviation. [b] One experiment. [c] 4-mm cell used.

Salt Effects.—Table II shows that there is a positive salt effect in the permanganate oxidation of I. This is consistent with the Debye–Hückel theory which predicts that a reaction between like charged ions will be accelerated by an increase in ionic strength.[14]

Cyclopentanenitronate Anion (II).—Table III summarizes the kinetic results for the oxidation of II. It is seen that k_2 is constant over a fivefold range of II concentration, and a plot of k_ψ *vs.* II gives a straight line that goes through the origin which indicates a first-order dependence on II. That the rate of oxidation is independent of pH is demonstrated by the constancy of k_2 over a 32-fold range of hydroxide ion concentration. A change in permanganate concentration over a fivefold range, at constant concentrations of II and hydroxide ion, does not alter k_ψ, which indicates a first-order dependence on permanganate. The rate law is the same as the one for I.

$$\frac{-d[MnO_4^-]}{dt} = 2k_2[\text{cyclopentanenitronate anion}][MnO_4^-]$$

Activation Parameters.—Table IV gives the thermodynamic data for the oxidation of I and II.

(14) Although the Debye–Hückel theory applies quantitatively only in dilute solutions, it can still be used to predict qualitatively the direction in which ionic strength influences reaction rates.

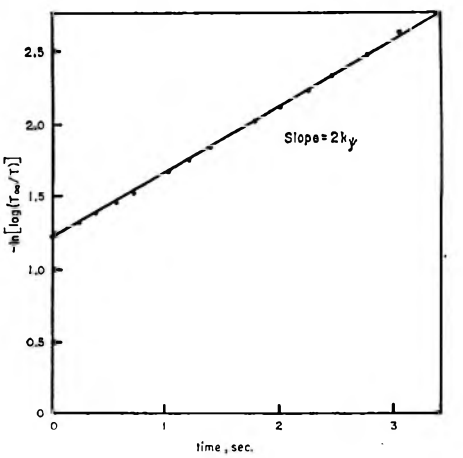


Figure 1—A typical kinetic plot.

TABLE II

KINETIC DEPENDENCE ON IONIC STRENGTH

([cyclohexanenitronate anion] = 4.0 × 10^{-3} M, [MnO$_4^-$] = 4.00 × 10^{-4} M, pH 13.0, T = 1.0 ± 0.02°, λ 522 mμ)

μ	$2k_\psi$ × 10^2 sec^{-1}
0.10	78 ± 2
0.30	102 ± 4
0.50[a]	122
0.75	148 ± 4
1.0	159 ± 1

[a] One determination.

TABLE III

KINETIC RESULTS FOR THE OXIDATION OF CYCLOPENTANENITRONATE ANION

(μ = 0.5 M, λ 522 mμ, T = 1.0 ± 0.02°, 10-mm cell)

[Cyclopentanenitronate anion] × 10^4 M	[OH$^-$], M	[MnO$_4^-$] × 10^4 M	$2k_\psi$ × 10^2 sec^{-1}	$2k_2$, M^{-1} sec^{-1}
20.0	0.10	4.00	12.3 ± 0.2	61.4
40.0	0.10	4.00	23.2 ± 0.2	58.1
55.6	0.10	4.00	32.7 ± 0.4	58.8
80.0	0.10	4.00	45.6 ± 1	57.1
100.0	0.10	4.00	54.5 ± 3	54.5
40.0	0.01	4.00	21.7 ± 0.2	54.2
40.0	0.032	4.00	24.2 ± 0.2	60.0
40.0	0.10	4.00	23.2 ± 0.2	58.1
40.0	0.32	4.00	24.2 ± 0.4	60.5
116.5[a]	0.10	4.00	45.1 ± 0.6	38.7
116.5[a]	0.10	6.00	48.8 ± 0.3	41.9
116.5[a]	0.10	8.00	49.9 ± 2	42.8
116.5[a]	0.10	10.00	48.9 ± 0.2	41.9
116.5[a]	0.10	12.00	49.3 ± 1	42.3

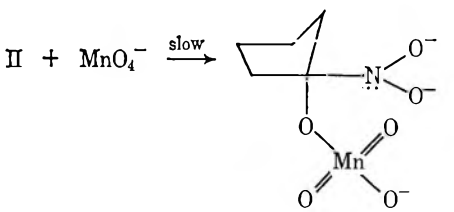
[a] 4-mm cell.

TABLE IV
ACTIVATION PARAMETERS FOR THE PERMANGANATE OXIDATION OF NITRONATE ANIONS

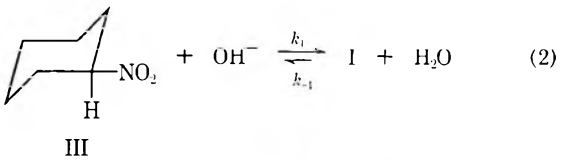
Substrate	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
I	7.45	−27.8
II	10.5	−20.0

Discussion

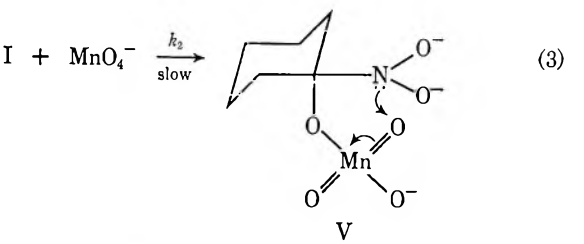
In basic solution nitrocycloalkanes form relatively stable nitronate anions[10-13] with unsaturated systems which are particularly vulnerable to nucleophilic attack.[15] The kinetic data suggest a scheme in which the nitronate anion is formed in an equilibrium step ($k_1 >>> k_{-1}$) and is oxidized by permanganate in the rate-determining step. A reasonable mechanism conforming to the observed kinetics would be[16,17] that given by reactions 2–5. The slow step (eq 3) is an attack of permanganate at the trigonal carbon of I or II to give the activated complex V or VII. This requires a change in rehybridization from sp^2 to sp^3 which predicts that II should react at a slower rate than I since the activated complex VII would be more strained (*I* strain[17-19]) than V. While there is considerable decrease in angular deformation in going from II to VII, the increased torsional strain in VII more than outweighs it, and the rate is decreased.



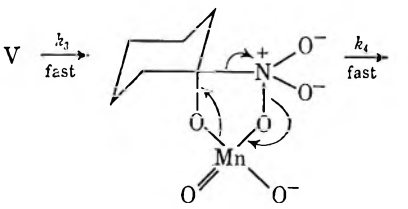
VII



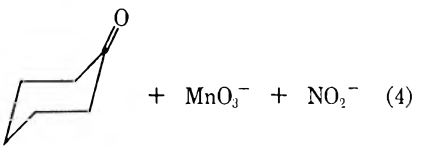
III

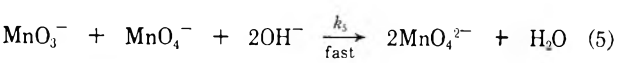


V



VI





An attempt to demonstrate this mechanism using permanganate ^{18}O was inconclusive owing to the rapid exchange of both cyclohexanone[20] and permanganate[21,22] with solvent in the strongly alkaline media.

Although the observed kinetic data are in agreement with the mechanism presented, it gives no information on alternate reaction pathways for the activated complexes. Further data on the kinetics of the possible subsequent steps as well as information on the steric requirements of the cycloalkylnitronate anions are under investigation.

Registry No.—I, 12349-47-2; II, 12349-48-3.

(15) I assumes the chair conformation and II probably assumes the *half-chair* conformation. See also F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(16) Alternatively, a *cis* cycloaddition of permanganate to I could give VI directly. However, the $\Delta S^{\ddagger}$ values, which are no doubt controlled largely by solvation effects, are not sufficiently negative to require a cyclic transition state. The significance of the magnitude of $\Delta S^{\ddagger}$ is further complicated by the fact that a vast majority of permanganate oxidations have large negative entropies of activation.

(17) Hypomanganate (MnO_3^-) is instantaneously oxidized by permanganate to manganate ion (MnO_4^{2-}) which slowly disproportionates to permanganate and manganese dioxide under the reaction conditions: F. R. Duke, *J. Phys. Chem.*, **56**, 882 (1952).

(18) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Amer. Chem. Soc.*, **73**, 212 (1951); H. C. Brown, *Rev. Chem. Progr.*, **14**, 83 (1953).

(19) The concept of *I* strain has been modified in recent times to include all strains from compression of van der Waals radii, bond opposition forces, and distortion of bond angles.

(20) K. Bieman, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 238.

(21) N. F. Hall and O. R. Alexander, *J. Amer. Chem. Soc.*, **62**, 3455 (1940).

(22) G. A. Mills, *ibid.*, **62**, 2833 (1940).

Cyclization of Ethyl Diallylacetate or Ethyl Diallylmalonate to Cyclopentane Derivatives during the Addition of Perfluoroalkyl and Trichloromethyl Radicals

NEAL O. BRACE

Department of Chemistry, Wheaton College, Wheaton, Illinois 60187

Received October 10, 1968

Radical cyclization reactions of 4-substituted 1,6-heptadienes were studied. Five- but not six-membered rings were obtained from iodoperfluoroalkanes or carbon tetrachloride with ethyl diallylacetate (I) or with ethyl diallylmalonate (II). Various derivatives of the cyclic adducts were prepared which confirmed the structures suggested by spectroscopic and other evidence. These reactions provide an entry into the area of partially fluorinated alicyclic carboxylic acids. Free-radical reaction of I with a variety of thiols or with diethyl phosphite is reported to have given five- *and* six-membered ring products; cyclopolymerization of II also is supposed to lead to six-membered ring structures.

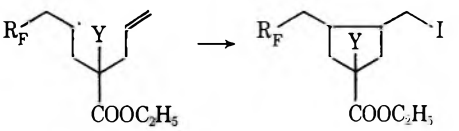
Cyclization of 1,6-heptadiene during the addition of perfluoroalkyl ($R_F\cdot$) radicals or trichloromethyl ($Cl_3C\cdot$) radicals gave substituted 1,2-dimethylcyclopentanes bearing various addenda.[1] This behavior has been recently observed[2] for the addition of the dialkyl phosphono radical[2] or $NF_2\cdot$ radical[3] to 1,6-heptadiene. A generalized pattern of reaction of 6-hepten-2-yl or 5-hexen-1-yl radicals seems to be emerging,[4-7] with a preference for five-membered ring formation. However, in a brief communication[8] in which reactions of ethyl diallylacetate (I) with n-$C_4H_9S\cdot$, $CH_3COS\cdot$, $C_2H_5O_2CCH_2S\cdot$, and $(C_2H_5O)_2P(O)\cdot$ radicals were given, six-membered ring products were reported to predominate over five-membered-ring compounds to the extent of two or three to one. Allusion was made to complex results from similar addition reactions involving related systems.[8] Other instances of five- and six-membered ring formation in free-radical cyclizations are known.[9] It seemed interesting and important, therefore, to determine if the addition of $R_F\cdot$ to I would give cyclization to five- *and* six-, or to only five *or* six-membered ring products. Analogous reaction of $CCl_3\cdot$ with I was also of interest. The related addition of $R_F\cdot$ radicals to ethyl diallylmalonate (II) was previously disclosed[1a] but is now described in detail. Cyclopolymerization of II has been stated[10,11] to give repeating units containing substituted cyclohexane rings, which have generally been accepted as the basic structural unit in analogous polymers.

Results and Discussion

As in previous cases studied[1] the $R_F\cdot$ radical [from R_FI, $R_F = CF_3CF_2CF_2$ or $CF_3(CF_2)_3$–] readily added to I or II with azonitrile initiator, giving an excellent yield of the substituted cyclopentane products (III or IV) and a much smaller amount of olefinic adducts (V or VI) (Scheme I). Bis adducts or telomers were not

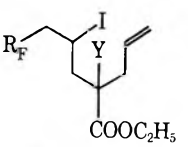
SCHEME I

R_FI + I or II →



III·, Y = H
IV·, Y = $COOC_2H_5$

III, Y = H
IV, Y = $COOC_2H_5$

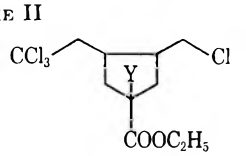


V, Y = H
VI, Y = $COOC_2H_5$

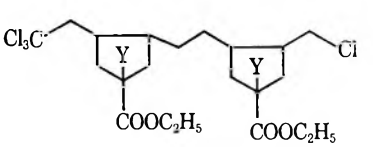
obtained under these conditions. Reaction of I or II with CCl_4 gave analogous products, VII, VIII, and also some telomer (IX), from II (Scheme II). The amount of

SCHEME II

CCl_4 + I or II →



VII, Y = H
VIII, Y = $COOC_2H_5$



IX, Y = $COOC_2H_5$

IX formed was very sensitive to reaction conditions, being greatly decreased when initiation by a Fe^{2+}/Fe^{3+} redox transfer system[1b,12] was used, or by increased

(1) (a) N. O. Brace, *J. Amer. Chem. Soc.*, **86**, 523 (1964); (b) *J. Org. Chem.*, **31**, 2879 (1966); (c) *ibid.*, **32**, 2711 (1967).
(2) N. O. Brace, to be published.
(3) S. F. Reed, *ibid.*, **33**, 1861 (1968).
(4) C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *J. Amer. Chem. Soc.*, **88**, 5361 (1966).
(5) R. F. Garwood, C. J. Scott, and B. C. L. Weedon, *Chem. Commun.*, 14 (1965).
(6) H. Pines, N. C. Sih, and D. B. Rosenfield, *J. Org. Chem.*, **31**, 2255 (1966).
(7) D. L. Struble, A. L. J. Beckwith, and G. E. Gream, *Tetrahedron Lett.*, No. 34, 3701 (1968).
(8) J. I. G. Cadogan, D. H. Hey, and A. Ong Soon Hock, *Chem. Ind.* (London), 753 (1964).
(9) M. Julia, J. M. Surzur, and L. Katz, *Bull. Soc. Chim. Fr.*, 1109 (1964); M. Julia and M. Maumy, *ibid.*, 434 (1966).
(10) S. G. Matsoyan, G. M. Pogosyan, and R. K. Skripnikova, *Chem. Abstr.*, **58**, 14107 (1963); *Vysokomol. Soedin.*, **4**, 1142 (1962); **5**, 183 (1963); *Chem. Abstr.*, **59**, 7654*b* (1964).
(11) C. D. Wright, U. S. Patent 3,247,170 (1966); *Chem. Abstr.*, **64**, 19923*a* (1966).
(12) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 2261 (1961); 1887 (1963); D. Vofsi and M. Asscher, *Org. Syn.*, **45**, 104 (1965).

CCl_4 concentration. These results are summarized in Table I. Little telomer was obtained from I and CCl_4 using the Fe^{2+}/Fe^{3+} catalyst system.

TABLE I

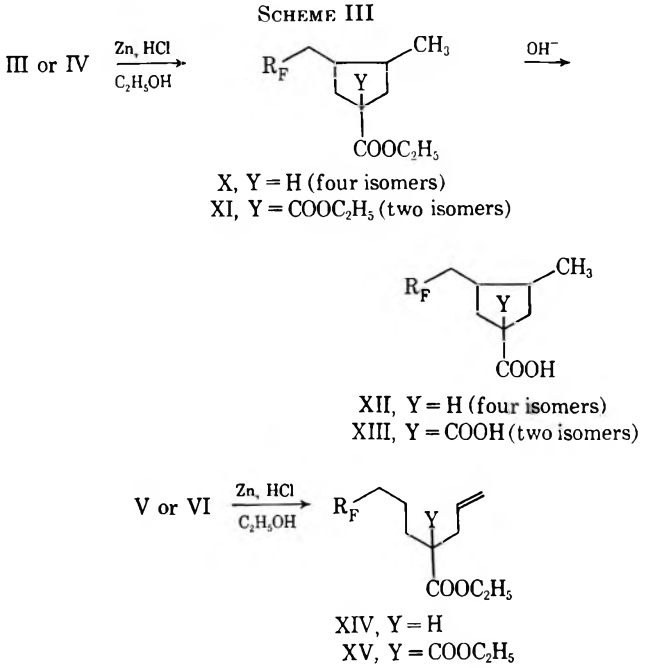
FREE-RADICAL REACTION OF CARBON TETRACHLORIDE AND II

CCl_4/II, mol	Reaction Time, hr	Reaction Temp, °C	Mol % initiator[a]	% convn VIII	% convn IX
1.2	12	82	1.8	20	49
2.4	12	82	3.7	55	28
5.0	16	82	2.0	68	18
5.0	22	77	(Fe^{3+})	87	8.4

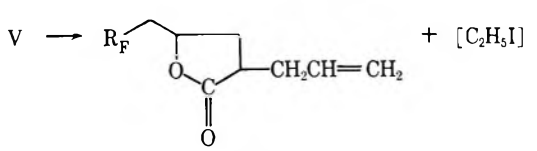
[a] Based on II.

A detailed study of the distribution of products from R_FI (or CCl_4) and I or II as a function of reaction conditions was not made since these high-boiling and heat-sensitive compounds could not be readily separated by distillation or by gas–liquid partition chromatography (glpc). Instead, product mixtures were converted into stable, distillable iodine-free derivatives by zinc reduction and the relative amounts of isomers (X and XIV or XI and XV, Scheme III) determined by glpc and nmr

SCHEME III



analysis. Little if any VI or XV was present in reaction products. One reason for the small amount of V observed in reaction product mixtures was that cyclization to a γ-lactone occurred during attempted isolation.[13] A sample of XVI was trapped from glpc separa-



XVI

tion and showed ir bands consistent with this structure ($\nu_{C=O}$ 1770 cm^{-1}; bands of CH_2=CH at 3090, 1640, 990 and 920 cm^{-1}).

(13) N. O. Brace, *J. Org. Chem.*, **29**, 1247 (1964).

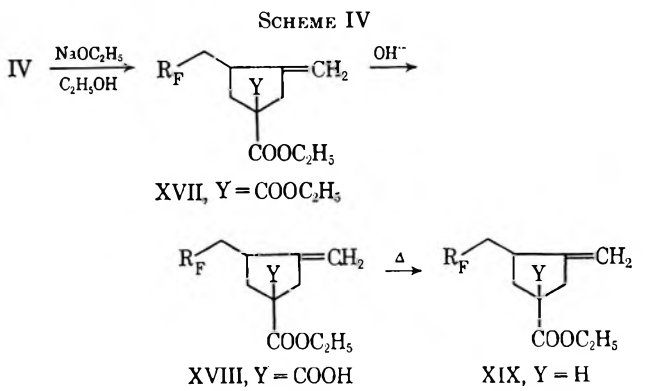
The methylcyclopentane structure of cyclic adducts III, IV, and their derivatives was clearly indicated by ir and nmr spectra. From the relative area of the proton resonances in nmr spectra and the number of peaks in glpc curves it was concluded that cyclohexane products were not present in significant amount on these reaction products.

For example, zinc reduction of a sample of III and V gave 92% yield of product containing isomers X and XIV, which was analyzed by glpc using five different columns. There were nine substances present in greater than 0.5% relative amount. However, the four isomers of X comprised 89% of the total, three early peaks (8% total) were olefinic compounds, I, XIV, and an unknown substance, and two later peaks (3%) were not identified. The possible amount of cyclohexane products in X could not have been greater than 5%. Similarly, zinc reduction of a reaction product containing IV (and possibly VI) gave reduced compounds in 94% yield, for which glpc analysis showed 19.3 and 76% *cis* and *trans* isomers of XI. An early peak (0.5%) and a late peak (2.8%) were not identified. Again the amount of cyclohexane isomers in XI could not have exceeded 5%.

Hydrolysis of samples containing X (four isomers) gave a mixture of acids, XII, with the corrent ratio for CH_3C– at δ 1.00 relative to COOH at δ 12.42 in nmr spectra. A cyclohexane–methylcyclopentane mixture could not have given this result. Hydrolysis of XI gave a crystalline isomer of XIII in 85% yield, again with the correct area for CH_3C– relative to COOH protons in nmr spectra. The oil residue was reconverted into ethyl esters and glpc showed formation of X isomers *via* decarboxylation. An acid chloride and amide from X isomers thus obtained were prepared in a separate experiment.

Reaction of IV with sodium ethoxide in anhydrous ethanol gave a mixture of dehydrohalogenation products in which XVII and XIX predominated. Reaction conditions were too vigorous to give clean reaction, and hydrolysis occurred in part to give XVIII which decarboxylated to XIX (Scheme IV). The CH_2=C

SCHEME IV

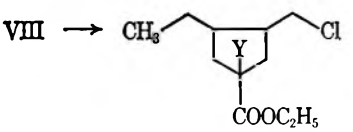


and $COOC_2H_5$ groups in XVII and XIX were shown by ir: ν_{CH} 3090, $\nu_{C=C}$ 1655, $\nu_{C=O}$ 1735, and $\gamma_{CH_2=C}$ 890 cm^{-1}. These are absorption bands unique to this structure,[14] which could not have been obtained from an isomeric cyclohexane product. Nmr spectra also

(14) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, Mass., 1966, pp 100–104.

displayed a clean doublet at δ 5.10, J = 7–8 Hz, indicative of the CH_2=C group.

Reduction of VIII by zinc gave a product bearing the CH_2Cl group. Nmr analysis showed proton resonances at δ 2.84 for CH_2CCl_3 and at δ 3.50 for CH_2Cl in VIII



XX, Y = $COOC_2H_5$

compared with δ 2.82 and δ 3.50 in the analogous 1-chloromethyl-2(2,2,2-trichloro)ethylcyclopentane from CCl_4 and 1,6-heptadiene.[1b] After reduction to XX nmr showed a CH_3 of ethyl at δ 1.00 and CH_2Cl at δ 3.50. Had the cyclization product VIII been a cyclohexane derivative there would have been a Cl_3CCH_2 but no $ClCH_2$ group present. By analogy with III and IV, it is believed that VII has a structure similar to VIII.

These data all are consistent with our previous results[1] showing cyclization of 6-hepten-2-yl radicals to five-membered rings. We are continuing our efforts to define more closely this radical cyclization process and must leave open the question of how and under what conditions cyclization to five- and six-membered rings from 1,6-heptadiene systems can occur.

It should be observed that synthesis of compounds such as III and IV from radical cyclizations presents a new and potentially valuable entry into interesting cyclopentylcarboxylic acid derivatives. A variety of substances having fluorinated or halogenated side chains and various functional groups can be readily prepared from the reactive intermediates III and IV, or from the analogous VII and VIII. The potential for new chemistry of these and related substances should be readily apparent.

Experimental Section[15]

Source of Materials.—1-Iodoperfluoropropane, Pierce Chemical Co., was redistilled, bp 40–41°, and kept cold before use. 1-Iodoperfluorobutane, bp 67°, $n^{25}D$ 1.3252, was a gift from E. I. du pont de Nemours and Co.

Ethyl Diallylacetate (I).—Ethyl allylacetoacetate was prepared:[16,17] bp 92–7° (12 mm); $n^{25}D$ 1.4360; 85% yield [lit.[18] bp 96–97° (14 mm); $n^{26}D$ 1.4365]. A slightly altered procedure gave this compound in 55% yield and a 14% yield of ethyl diallylacetoacetate: bp 112° (12 mm); $n^{25}D$ 1.4540. However, reaction of allyl bromide with ethyl allylacetoacetate by the same procedure gave alcoholysis of the aceto group[19] and a 73% yield of I: bp 85° (21 mm); $n^{25}D$ 1.4352 (lit.[20] bp 189–191°; $n^{20}D$ 1.4364); ir (CCl_4) $\nu_{CH=CH}$ 3090, ν_{CH} 2890, $\nu_{C=O}$ 1730, $\nu_{C=C}$ 1640, $\gamma_{=CH}$ 995, 920 cm^{-1}. Elemental analysis also was consistent. Glpc (6 ft × 0.25 in. Carbowax 20M, 20% on Chromosorb W, at 160°) gave 99% area under one peak.

Ethyl Diallylmalonate (II).—Ethyl malonate was alkylated with 2 equiv of allyl bromide.[16] Fractional distillation using column A gave ethyl allylmalonate (7%) and II: bp 129° (15 mm); $n^{25}D$ 1.4436 (79%) [lit.[21] bp 120–122° (12 mm); $n^{20}D$ 1.4435].

Ethyl 3-Iodomethyl-4-(perfluoropropyl)methylcyclopentyl-1-carboxylate Isomers (III).—1-Iodoperfluoropropane (60.0 g, 0.20 mol), I (16.8 g, 0.10 mol) and azobis-2-methyl-2-propionitrile ABN (0.26 g, 0.0015 mol) were charged to a Fischer–Porter aerosol tube, purged with nitrogen and evacuated to 0.1 Torr at −78° three times and heated in an oil bath at 70° for 21.5 hr. The reaction mixture became brown in 1 hr. The tube when cool was opened, 1-iodoperfluoropropane, 31.8 g, pumped off into a trap at −70° and the product (A), 43.5 g, distilled in column A, using an oil bath. Iodine was formed. Fractions taken were (1) bp 42° (0.15 mm), $n^{20.5}D$ 1.4352, 2.9 g, I, 17.3% recovery; (2) bp 72–88° (0.15 mm), $n^{20.5}D$ 1.4316, 4.6 g, a mixture of I, III, V and other substances; (3) bp 92° (0.15 mm), $n^{20.5}D$ 1.4400, 17.3 g; (4) 92–94° (0.13 mm), $n^{20.5}D$ 1.4390, 14.0 g; (5) residue, 0.2 g. Cuts 3 and 4 comprised isomers of III (67% conversion), with essentially no bis adduct or telomeric products being formed. An ir spectrum (neat) of 3 and 4 showed no detectable unsaturation but bands listed below for III. Product B from a second run was distilled without a column: bp 30–33° (0.13 mm), 2.25 g, 13.5% recovery of I; and bp 90–93° (0.13 mm), $n^{25}D$ 1.4379, 34.8 g, 73% conversion into cyclic isomers; residue 1.2 g. Samples of product B and fractions 3 and 4 gave identical nmr spectra (neat): δ 1.23, CH_3CH_2O (t, J = 7 Hz, 3.04 H); δ 1.24–3.00, R_FCH_2CH, $(CH_2)_2CH$–, CH (unresolved, 8.85 H); δ 3.22, CH_2I (unresolved, 2.05 H); δ 4.10, CH_3CH_2O (q, J = 7 Hz, 1.88 H). There were no olefinic proton resonances. The $-CH_2I$ resonance appeared at δ 3.25 in a product of similar structure.[1b] Infrared spectra of product B showed that a small amount of V was present (weak olefinic bands), and the bands of III isomers: ν_{CH} 2980, 2960, 2910, 2870; $\nu_{C=O}$ 1730; δ_{CH} 1450 and 1380 (CH_3), 1440, 1365, 1345; and bands at 1230, 1200, 1185, 1120 (COC), 1065, 1030, 1010, 958, 925, 860, 760, 730 and 710 cm^{-1}. Glpc analysis was attempted with a variety of columns and conditions to determine the relative amounts of isomers present, and a 6 ft × 0.25 in., 10% QF-1 fluorosilicone oil on Chromosorb WA (DMAC treated) column, run at 185° and 25-psi helium pressure, was selected. Glpc of fraction 2 gave 0.9 min, 3.59% (I); 2.5 min, 2.76%; 3.2 min, 23.2% (probably V); 3.6 min, 23.6% (probably a γ-lactone (XVI) derived from V; see below for ir); 4.8 min, 9.55%; 10.1 min, 28.7%, an isomer of III; 11.1 min, 5.24% (same); 13.5 min, 3.3% (same). Fractions 3 and 4 contained only isomers of III in varying ratios. The various peaks were trapped and ir spectra recorded using a microcell (AgCl plates). Insufficient amount of V was isolated for complete characterization; ir showed olefinic bands at 3090, 1640, 990 and 920 cm^{-1} (CH_2=CH–), $\nu_{C=O}$ 1735 cm^{-1}, CH_3, CH_2, and COC absorption bands in the peak trapped. XVI gave bands at 3090, 1640, 990 and 920 cm^{-1} (CH_2=CH—); $\nu_{C=O}$ 1770 cm^{-1} (strong); δ_{CH} 1450, 1440, 1400 and 1350, but no δ_s of CH_3 at 1370 cm^{-1}; CF bands 1280, 1220; COC bands at 1180 and 1120; and bands at 960, 790, 745, 735, 700, 660 and 635 cm^{-1}. Product B showed 0.85% of I, 2.4% each of peaks at 3.2 and 3.6 min, and 94% of four peaks of III isomers at 10.1–16.8 min. A major part of III isomers decomposed on a Carbowax 20M (20%) on Chromosorb WA column at 185°. The mixture of substances trapped included (from ir) XV and III isomers. The trapped isomers of III were analyzed.

Anal. Calcd for $C_{13}H_{16}F_7O_2I$: C, 33.6; H, 3.47. Found (cut 3): C, 33.9; H, 3.55.

Ethyl 3-Methyl-4-(perfluoropropyl)methylcyclopentyl-1-carboxylate Isomers (X) and Ethyl 2-Allyl-6,6,7,7,8,8,8-heptafluorooctanoate (XIV).—Distilled product B above (34.0 g, 0.073 mol), ethanol (125 ml), and zinc (20–40 mesh, 6.5 g, 0.10 g-atom) were stirred rapidly while being saturated with hydrogen chloride at 75–80°. The yellow slurry began to foam, and became colorless after 15 min. Additions of zinc (three 3.0-g samples) were made after 15 min, 1 hr, and 1.5 hr. The colorless solution was decanted into 150 ml of water and extracted three times with a 1:1 mixture of benzene and ether. The organic extract was rinsed with sodium sulfite solution and with

(15) Melting points were determined with a Thomas–Hoover Unimelt apparatus. Infrared spectra were obtained with a Perkin-Elmer Model 337 grating spectrophotometer. Nmr spectra were obtained from neat samples with a Varian A-60 instrument at ambient temperature and are reported in parts per million from tetramethylsilane as an internal standard. Integrated areas measured by the instrument are given as number of H, calculated from the empirical formula and the total area. Distillations were done in a 16-in. Nester–Faust stainless steel spinning-band column (column A). Gas chromatographic analyses (glpc) were done with a Microtek 1500 instrument using columns and conditions indicated. Per cent relative areas were measured by a disk integrator on the recorder.

(16) "Organic Syntheses," Coll. Vol. I, H. Gilman and A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1947, p 250.

(17) A. C. Cope, K. E. Hoyle, and D. Heyl, *J. Amer. Chem. Soc.*, **63**, 1843 (1941).

(18) M. S. Schechter, N. Green, and F. B. LaForge, *ibid.*, **71**, 3165 (1949).

(19) *Cf.* ref 17 where reaction time was limited to 0.5 hr, even though reaction was incomplete, to reduce alcoholysis.

(20) K. Auwers and W. Moosbrugger, *Ann.*, **387**, 167 (1912).

(21) R. Ya Levina and N. N. Godovikov, *Zh. Obshch. Khim.*, **24**, 1572 (1954); *Chem. Abstr.*, **49**, 11667 (1955).

water, dried over $MgSO_4$ and distilled without a column: bp 71–83° (1.25–0.50 mm); $n^{25}D$ 1.3825, 22.8 g (92%). Glpc, 6 ft × 0.25 in. XE-60 silicone resin (15%) on Chromosorb WA column at 145°, with 25-psi helium pressure, showed retention times, relative areas: (1) 6.0 min, 0.4%; (2) 7.0 min, 1.5%; (3) 11.1 min, 6.4%; (4) 13.8 min, 10.6%; (5,6) 17.0 min, 52.7% (two peaks); (7) 18.8 min, 25.3%; (8) 22.6 min, .83%; (9) 25.2 min, 2.27%. Peak 1 was I; peaks 2 and 3 were XIV and another olefinic compound since ir showed CH_2=CH– bands at 3090, 1640, 995, 910, $\nu_{C=O}$ at 1730, and other identical bands; peaks 4–7 were isomers of X (four possible); and peaks 8 and 9 were unknown. A portion of the product, 10.9 g, was redistilled in column A: cut 1, bp 98–107° (11 mm), $n^{25}D$ 1.3876, 1.1 g; cut 2, bp 110° (11 mm), $n^{25}D$ 1.3829, 6.9 g; cut 3, bp 108° (9 mm), $n^{25}D$ 1.3836, 2.1 g; column holdup, 0.6 g. These cuts were examined by ir, nmr, and glpc. Ir (cut 3) showed ν_{CH} 2960, 2920, 2880; $\nu_{C=O}$ 1730; δ_{CH} 1460, 1450, 1440, 1430, 1380, 1370, 1350, ν_{CF} 1280–1260; bands at 1170, 1120, 1080, 1050, 1000, 960, 925, 850, 760, 720 (s), 630, 540, and 520 cm^{-1}. Glpc (QF-1 fluorosilicone oil column at 150°, 15-psi helium pressure): cut 1 gave (1) 2.8 min, 12.9%; (2) 4.0 min, 0.75%; (3) 5.1 min, 7.45%; (4) 7.4 min, 19.4%; (5) 9.3 min, 13.5%; (6) 11.0 min, 39.6%; (7) 12.0 min, 9.2%; cut 2 showed 7.2% of peak 3 and the remainder of peaks 4–7; cut 3 gave only peaks 4–7 and 0.66% of a later peak. Cut 1 nmr showed δ 0.8–1.0, CH_3CH (two d, 1.7 H); δ 4.7–6.4, CH_2=CH– (m, 1.5 H); ir ν_{CH} 3090, 1640; $\nu_{C=O}$ 1735. Cuts 2 and 3 had δ 0.9 CH_3CH (d, J = 7 Hz, 3.08 H); δ 1.20, CH_3CH_2O (t, J = 7 Hz, 3.4 H); δ 1.2–2.6 $(CH_2)_2CH$, R_FCH_2CH and CH_3CH (unresolved, 7.85 H); δ 2.85, $CHCOOC_2H_5$ (t, J = 7 Hz, 1.0 H); δ 4.15 CH_3CH_2O (q, J = 7 Hz, 1.7 H). These data confirm that cut 1 contained I, XIV and isomers of X, and that cuts 2 and 3 were substantially pure isomers of X. Careful refractionation in column A was unsuccessful in separating isomers of X, bp 115° (20 mm); only four peaks appeared in glpc analysis, also run on a 6 ft × 0.25 in. cyanosilicone oil (XE 60, 15%), on a Chromosorb WA column at 145° and 25-psi helium, and on Carbowax 20M, "Craig polyester" and "FFAP" columns under similar conditions. Samples of X and XIV from cut 1 were trapped from glpc separation on the QF-1 column. Peak 4 at 7.4 min was XIV: ir ν_{CH} 3090, 2990, 2950, 2880; $\nu_{C=O}$ 1730; $\nu_{C=C}$ 1640; δ_{CH} 1455, 1435, 1370, 1350; bands at 1250–1170, 1120, 1020, 995, 960, 950, 920, 910, 880, 850, 785, 750, 730, 700, 650, 640, 555, 550 and 535 cm^{-1}. Bands at 3090, 1640, 995 and 910 revealed the vinyl group; all the other bands were consistent with the structure of XIV.

Anal. Calcd for $C_{13}H_{17}F_7O_2$: C, 46.15; H, 5.07. Found (XIV): C, 46.08; H, 4.95. Found (X isomers): C, 46.3; H, 5.24.

Preparation of 3-Methyl-4-(perfluoropropyl)methylcyclopentyl-2-carboxylic Acid Isomer Mixture (XII).—Mixture of X isomers (10.0 g, 0.0325 mol) and KOH (3.36 g, 0.06 mol) dissolved in 90% aqueous ethanol (56 ml) was kept at 80° for 7.8 hr, diluted with 100 ml of water, acidified with 10 ml of concentrated HCl and extracted three times with ether. The ether extract was dried ($MgSO_4$) and evaporated off, leaving 8.8 g (84%) of XII isomer mixture. Fractional distillation in column A gave cuts: (1) bp 98–107° (1.5 mm), $n^{25}D$ 1.3894, 1.2 g; (2) bp 110° (1.2 mm), $n^{25}D$ 1.3872, 2.65 g; (3 and 4) bp 100° (0.30 mm), $n^{25}D$ 1.3882, 3.7 g (no residue). Cuts 2 and 3 (5% in CCl_4) gave ir $\nu_{COOH,CH}$ 3100–2880; $\nu_{C=O}$ 1705; δ_{CH_3} 1450, 1380; $\delta_{CH_2,CH}$ 1470, 1430, 1420, 1350; bands at 1230, 1203, 1180, 1140, 1070, 1050, 980 (sh), 965, 925, 690, 645, 550 and 530 cm^{-1}; nmr neat δ 1.00, CH_3CH (overlapping doublets, 3.02 H measured by hand and machine); δ 1.6–2.7, $(CH_2)_3$ and $(CH)_2$ (m, unresolved, 8.0 H); δ 2.7–3.55, –CHCOOH (t, J = 7 Hz, 1.0 H); δ 12.42, COOH (s, 1.0 H). No vinyl proton resonances appeared; XII isomeric structures were confirmed by relatives areas of CH_3 and COOH groups. Cut 1 contained X, XII and some olefinic substances according to nmr.

Anal. Calcd for $C_{11}H_{13}F_7O_2$: C, 42.58; H, 4.22. Found: C, 42.76; H, 4.30.

Ethyl 3-Iodomethyl-4-(perfluoropropyl)methylcyclopentyl-1,1-dicarboxylate (IV).—1-Iodoperfluoropropane (60.0 g, 0.20 mol), II (16.8 g, 0.069 mol), and ABN (0.32 g, 0.0020 mol) were heated at 70° for 24 hr as previously done with III. 1-Iodoperfluoropropane (37.4 g, 96%) was recovered, leaving residual oil, 35.4 g (95%): ir (no CH_2=CH bands) ν_{CH} 2980, 2940, 2920, 2880; $\nu_{C=O}$ 1735; δ_{CH} 1460, 1440, 1380, 1360 and 1350; bands at 1260, 1220, 1180, 1100, 1065, 1045, 1030, 990 (shoulder), 960, 930, 860, 760, 730 and 715 cm^{-1}. A 2:1 reactant ratio gave 93% yield of IV. Distillation from an oil bath in a short-path still gave IV: R_F = $CF_3CF_2CF_2$–; bp 132° (0.25 mm); $n^{22}D$ 1.4402; 32.6 g (88%); residue 1.0 g. A portion, 6.3 g, redistilled in column A: bp 118° (0.15 mm); $n^{22.5}D$ 1.4404; 5.7 g; ir same as above; nmr δ 3.17, CH_2I (m, 2.3 H), and no olefinic protons.

Anal. Calcd for $C_{16}H_{20}F_7IO_4$: C, 35.8; H, 3.76; F, 24.8. Found: C, 36.1; H, 3.87; F, 25.2.

1-Iodoperfluorobutane and II gave IV: R_F = $CF_3(CF_2)_3$–; bp 116° (0.20 mm); $n^{25}D$ 1.4295; 26.4 g (95%); ir $\nu_{C=O}$ 1735 cm^{-1} and no olefinic bands.

Anal. Calcd for $C_{17}H_{20}F_9IO_4$: C, 34.83; H, 3.44; I, 21.65. Found: C, 34.8; H, 3.5; I, 21.5.

Ethyl 3-Methyl-4-(perfluoropropyl)methylcyclopentyl-1,1-dicarboxylate (XI).—Zinc reduction of IV, R_F = $CF_3CF_2CF_2$– (19.0 g, 0.0365 mol), was done as above with III. XI, R_F = $CF_3CF_2CF_2$–, 14.0 g, 94%, was distilled without a column: cut 1, bp 88–110° (1.30 mm), $n^{25}D$ 1.3983, 1.55 g; 2, bp 110–112° (1.00 mm), $n^{25}D$ 1.3964, 10.0 g; 3, holdup, $n^{25}D$ 1.3975, 0.45 g; and residue, 1.5 g (80% yield); ir, neat, KBr plates, ν_{CH} 2970 cm^{-1}, ν_{as} CH_3; ν_s CH_3 at 2870 was stronger in XI than in IV; $\nu_{C=O}$ 1735 cm^{-1}. Glpc, using a 6 ft × 0.25 in. Carbowax 20M (10%) on Chromosorb W at 178°, with 25-psi helium, gave peaks: cut 1, 7-min retention time, 0.25%; 8.8 min, 0.15%; 11.1 min, 19.2%; 13.4 min, 79.5%. Cut 2 gave 11.2 min, 20.5%; 13.4 min, 79.5%. Cut 3 gave 11.1 min, 4.7%; 13.4 min, 94%; 17.5 min, 1.6%. The isomer ratio in XI based on relative areas was thus 20:80; nmr (neat) δ 0.90, CH_3CH– (d, J = 6 Hz, 2.2 H); δ 1.2, $(CH_3CH_2O)_2$ (t, J = 7 Hz, 5.1 H); δ 1.87, CH_3CH– (m, unresolved, 1 H); δ 2.0–2.8, $(CH_2)_2$ and R_FCH_2CH– (m, 8.0); δ 4.14, $(CH_3CH_2O)_2$ (q, J = 7 Hz, 4.0 H).

Anal. Calcd for $C_{16}H_{21}F_7O_4$: C, 46.71; H, 5.38. Found: C, 46.31; H, 5.10.

Ethyl 3-methyl-4-(perfluorobutyl)methylcyclopentyl-1,1-dicarboxylate (XI) [R_F = $CF_3(CF_2)_3$–] was obtained from IV in 90% yield, bp 112–114° (1.2 mm), $n^{25}D$ 1.3896.

Anal. Calcd for $C_{17}H_{21}F_9O_4$: C, 44.36; H, 4.60; F, 37.15. Found: C, 44.5; H, 4.6; F, 37.2.

3-Methyl-4-(perfluoropropyl)methylcyclopentyl-1,1-dicarboxylic Acid (XIII).—XI (8.2 g, 0.020 mol) was added to a solution of KOH (2.24 g, 0.040 mol) in 90% aqueous ethanol (50 ml) and heated at 80° for 10 hr. At 25° water (100 ml) and concentrated HCl (7 ml) were added; the mixture was extracted three times with ether. The ether extract was dried ($MgSO_4$) and evaporated off giving solid XIII: R_f = $CF_3CF_2CF_2$–, 6.9 g, 97%, mp (sinter 103°) 115–125° dec. Essentially all the solid dissolved at the boil in CCl_4 (125 ml), and at 25° deposited 5.95 g of XIII (84%), mp 132.2–132.9°. Recrystallization again from CCl_4 (125 ml) gave 5.93 g of XIII, mp 129.5–130.5°. The filtrates evaporated off gave an oil (0.9 g) which was soluble in ligroin. It was reesterified with ethanol, taking off the ternary azeotrope with benzene. Glpc analysis (6 ft × 0.25 in. Carbowax 20M, 20% on Chromosorb W, 192°, 20-psi helium) gave (1) 2.0 min, 35.6%; (2) 4.0 min, 4.55%; (3) 5.0 min, 2.60%; (4) 5.70 min, 10.4%; (5) 6.75 min, 40.1%; (6) 8.50 min, 6.78%. Peaks 2, 4, 5, and 6 were present in the original mixture. By comparison with a known sample of X isomers run under these conditions, peak 1 was an isomer of X, formed by decarboxylation of XIII and reesterification. Peaks 4 and 5 were isomers of XI, recovered in altered ratio from the original mixture. The solid XIII was evidently isolated in only one isomeric form.

An nmr spectrum of XIII was obtained from 0.26 g in 0.30 ml of acetone-d_6. Insufficient sample dissolved in $HCCl_3$ or CCl_4 to give a spectrum. Resonances were at δ 0.90, CH_3CH– (3.1 H); δ 1.8–3.0, $(CH_2)_3$ and $(CH)_2$ (m, not resolved, 8.2 H); δ 10.8, $(COOH)_2$ (s, 2.0 H); the ratio of CH_3 to COOH again confirmed the postulated structure; ir (KBr disk) ν_{CH} 2975, 2925 (CH_3, CH_2); $\nu_{C=O}$ 1697; δ_{CH_3} 1450; bands at 1430, 1400, 1350, 1280, 1226, 1170, 1110, 960, 922 and 740 cm^{-1}. Titration with 0.0100 N KOH solution using a pH meter gave breaks at pH 5.15 and pH 9.30; neut equiv, 204 (202 theory).

Anal. Calcd for $C_{12}H_{13}F_7O_4$: C, 40.68; H, 3.69; F, 37.54. Found: C, 40.4; H, 3.59; F, 37.4.

3-Methyl-4-(perfluorobutyl)methylcyclopentyl-1,1-dicarboxylic acid, XIII (R_f = $CF_3CF_2CF_2CF_2$), was obtained in similar fashion from XI in 87% yield, mp (sinter 92–99°) 108–120°. A sample (5.0 g) was recrystallized from 1,1,2-trichloro-1,2,2-trifluoroethane ("F-113", 30 ml) and then from benzene,

4.0 g, mp 130–132° (gas evolution). A residual oil (0.46 g) was recovered: nmr (α,α'-dichlorotetrafluoroacetone dihydrate) δ 0.92, CH_3CH– (m, unresolved, 3 H); δ 1.70–2.8, $(CH_2)_3$ and $(CH)_2$ (m, unresolved, 8 H); ir (KBr disk) gave a spectrum very similar to XIII, $R_F = CF_3CF_2CF_2$.

Anal. Calcd for $C_{13}H_{13}F_9O_4$: C, 38.6; H, 3.24; F, 42.3. Found: C, 38.3; H, 3.2; F, 42.3.

Preparation of 3-Methyl-4-(perfluorobutyl)methylcyclopentyl-1-carboxamide.—XIII ($R_f = CF_3CF_2CF_2CF_2$, 2.02 g, 0.0050 mol) in xylene (10 ml) was heated to reflux for 23 hr, giving evolution of carbon dioxide. Solid did not separate from the clear yellow solution upon cooling, but an oily mixture of XII isomers (1.8 g, 95%) was obtained by evaporation. The oil was heated with 5.0 ml of thionyl chloride for 2 hr at 80°; the acid chloride of XII isomers was distilled, bp 108–114° (10 mm), 1.3 g (69%), and poured slowly while stirring into 5.0 ml of concentrated ammonium hydroxide at 0°. White solid amide of XII was collected, washed with water and dried, 1.25 g (100%), mp (sinter 99°) 102–103°. The XII amide ($R_F = CF_3CF_2CF_2CF_2$) was recrystallized from methylcyclohexane, 0.90 g, mp 104–105°, and 0.05 g, mp 101–103.5°.

Anal. Calcd for $C_{12}H_{14}F_9NO$: C, 40.0; H, 3.94. Found: C, 40.0; H, 3.96.

Ethyl 3-Methylene-4-(perfluoropropyl)methylcyclopentyl-1,1-dicarboxylate (XVII) and Ethyl 3-Methylene-4-(perfluoropropyl)-methylcyclopentyl-1-carboxylate (XIX).—Adduct mixture IV (24.9 g, 0.04 mol) was added to a solution of sodium ethoxide prepared from sodium (5.8 g, 0.25 g-atom) in ethanol (100 ml). The temperature rose to 65° and then to 89° when warmed externally; the mixture became dark brown. It was cooled to 52°, kept for 4 hr, and poured into 300 ml of water. Hydrochloric acid (6 *N*, 50 ml) was added, extracted three times with ether, and the ether extracts were rinsed with water, dried ($MgSO_4$), and distilled. The distilled product mixture [bp 135–150° (20 mm), 10.3 g] was fractionated in column A. Cuts 1, 2, and 3, bp 107–127° (12 mm), 3.3 g, contained XIX (21% conversion) and some XVII. Cuts 4, 5, and 6, bp 120–2° (3.2 mm), $n^{25}D$ 1.4020, 7.4 g, were principally XVII (40% conversion). Cuts 1–3 were refractionated to give pure XIX, bp 105° (11 mm), $n^{25}D$ 1.3930. Reaction of IV (0.03 mol) and sodium ethoxide (0.04 mol) in ethanol at 29–30° for 15 hr also gave a mixture of XVII (37%) and XIX (13%). Glpc analysis (QF-1 column, 150°, 30 psi) showed 99% under a peak at 4.3 min (XIX); and 99% under one peak at 20.6 min for XVII in cut 5. At a slower flow rate (15-psi helium pressure) refractionated XIX gave 95.9% at 11.8 min and 4.1% at 19.4 min: XVII, ir ν_{CH} 3090, 3000, 2950, 2920 and 2880; $\nu_{C=O}$ 1730; $\nu_{C=C}$ 1655; δ_{CH} 1470, 1450, 1430, 1380, 1370 and 1350; bands at 1260, 1180, 1120, 1070, 1045, 1020, 960, 930, 890, 860, 760, 725, 715, 660, 650, 550 and 530 cm^{-1}. The ir spectrum of XIX was identical with XVII's from 3090 to 1100 cm^{-1}, but gave bands at 1040, 960, 925, 890, 860, 822, 760, 725, 715, 660, 650, 550 and 530 cm^{-1}. The carbonyl band at 1730 was stronger in XVII, but bands at 1650 and 890 (C=CH_2) were stronger in XIX than in XVII, as would be expected from the difference in structure. The nmr spectrum of XVII showed CH_3CH_2O at δ 1.25 (t, J = 7 Hz, 6.1 H) and 4.30 (q, J = 7 Hz, 3.9 H); CH_2=C, δ 5.10 (d, J = 8 Hz, 1.8 H). The nmr spectrum of XIX showed CH_3CH_2O at δ 1.25 (t, J = 7 Hz, 3.2 H) and 4.21 (q, J = 7 Hz, 2.0 H); R_FCH_2CH–, δ 1.9 (t, J = 7 Hz, 1.0 H); $(CH_2)_2CH$, R_FCH_2, δ 1.9–3.4 (m, unresolved, 6.7 H); CH_2=C, δ 5.08 (d, J = 7 Hz, with additional 1-Hz splitting with protons on the ring, 1.9 H).

Anal. Calcd for $C_{16}H_{19}F_7O_4$ (XVII): C, 47.06; H, 4.69. Found: C, 47.05; H, 4.63.

Anal. Calcd for $C_{13}H_{15}F_7O_2$ (XIX): C, 46.43; H, 4.50; F, 39.55. Found: C, 46.60; H, 4.58; F, 39.23.

Ethyl 3-Chloromethyl-4-(2,2,2-trichloroethyl)cyclopentyl-1,1-dicarboxylate (VIII).—CCl_4 (77.0 g, 0.50 mol), II (24.0 g, 0.10 mol), and a solution of acetonitrile (8.2 g, 0.20 mol), ferric chloride hexahydrate (0.27 g, 0.001 mol), benzoin (0.21 g, 0.002 mol), and diethylamine hydrochloride (0.16 g, 0.0015 mol) were charged to a Fischer–Porter aerosol tube, purged by CO_2 from a piece of Dry Ice, and heated at 77° for 22 hr. The contents were extracted with 5% aqueous hydrochloric acid (25 ml) and dried ($MgSO_4$). VIII was distilled in a short-path still, bp 149–155° (0.15–0.25 mm), with the oil-bath temperature up to 192°; $n^{22}D$ 1.4929; 34.2 g (87%); residue, 2.6 g. Reaction induced by 2 mol % ABN gave 68% of VIII and telomer IX (5.8 g) too high boiling to distil. Elemental analysis and physical properties were consistent with this formulation of IX. VIII was redistilled: bp 145° (0.08 mm); $n^{22}D$ 1.4930; ir (CCl_4) ν_{CH} 2980, 2960, 2910, 2870; $\nu_{C=O}$ 1725; δ_{CH} 1475, 1460, 1440, 1425, 1370, 1360; bands at 1300, 1260, 1180, 1160, 1110, 1070, 1040, 935, 860, 800, 730, 705 cm^{-1}; nmr (10% in CCl_4) δ 1.24 $(CH_3CH_2O)_2$ (t, J = 7 Hz, 6 H); δ 2.2–2.4, $(CH_2)_2$ and $(CH)_2$ (m, unresolved, 5.5 H); δ 2.84, CH_2CCl_3 (m, 2.2 H); δ 3.50, CH_2Cl (m, 2.2 H); and δ 4.13, $(OCH_2CH_3)_2$ (q, J = 7 Hz, 3.8 H).

Anal. Calcd for $C_{14}H_{20}O_4Cl_4$: C, 42.66; H, 5.12; Cl, 35.85. Found: C, 42.8; H, 5.15; Cl, 36.1.

Anal. Calcd for $C_{28}H_{40}O_8Cl_4$ (n = 2 telomer): Cl, 22.7. Found: Cl, 24.8.

Zinc Reduction of VIII to Ethyl 3-Chloromethyl-4-ethylcyclopentyl-1,1-dicarboxylate (XX).—VIII (22.3 g, 0.058 mol) and ethanol (140 ml) was stirred vigorously while anhydrous hydrogen chloride was bubbled in at 75°, and zinc (20 mesh, 26 g, 0.4 g-atom) was added in four portions during 1 hr; the mixture foamed while stirring and gassing with HCl was continued for 17 hr. The liquid was decanted into 200 ml of water and extracted with ether and benzene four times; the organic layer was washed with 5% bicarbonate solution, with water and dried ($MgSO_4$). Fractionation in column A gave XX: bp 110° (0.20 mm); $n^{21.5}D$ 1.4630; 10.7 g (65%); brown oil residue, 4.1 g (18.5% as VIII); ir ν_{CH} 2960, 2870 CH_3 stronger in XX than in VIII; no band at 705 cm^{-1} in XX; other bands very similar; nmr δ 1.00, CH_3CH_2 (m, partially obscured by adjacent proton resonance, 3.1 H); δ 1.2, CH_3CH_2O (t, J = 7 Hz, 6.5 H); δ 1.8–2.8, $(CH_2)_2$, CH_2CH_3 and $(CH)_2$ (m, unresolved, 7.9 H); δ 3.50, CH_2Cl (m, 2.1 H); δ 4.12, OCH_2CH_3 (q, J = 7 Hz, 3.9 H).

Anal. Calcd for $C_{14}H_{23}ClO_4$: C, 57.8; H, 7.97; Cl, 12.2. Found: C, 58.0; H, 8.1; Cl, 12.0.

Ethyl 3-Chloromethyl-4-(2,2,2-trichloro)ethylcyclopentyl-1-carboxylate (VII).—CCl_4 (77.0 g, 0.50 mol), I (16.8 g, 0.10 mol), and acetonitrile–$FeCl_3 \cdot 6H_2O$–benzoin–diethylamine hydrochloride exactly as above reacted at 79° for 20 hr gave 27.2 g (84%) of a yellow oil. An 11.1-g portion was distilled in a short-path sublimer apparatus at 90–110° (0.10 mm), $n^{24}D$ 1.5031; and at 98–112° (0.05 mm), $n^{24}D$ 1.5048; less than 0.1 g remained undistilled; ir (CCl_4) ν_{CH} 2980, 2960, 2945, 2920, 2875; $\nu_{C=O}$ 1730; δ_{CH} 1470, 1460, 1440, 1380, 1360, 1345; bands at 1290, 1280, 1180, 1160, 1095, 1035, 920, 880, 860, 700 and 580 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}Cl_4O_2$: C, 41.0; H, 5.00. Found: C, 41.0; H, 5.06.

Registry No.—I, 18-325-74-1; II, 3195-24-2; III ($R_F = CF_3CF_2CF_2$), 20116-37-4; IV ($R_F = CF_3CF_2CF_2$), 20116-24-9; IV [$R_F = CF_3(CF_2)_3$–], 20147-88-0; VII, 20116-25-0; VIII, 20116-26-1; VIII (n = 2 telomer), 20116-27-2; X ($R_F = CF_3CF_2CF_2$–), 20116-28-3; XI [$R_F = CF_3CF_2CF_2$–], 20116-29-4; XI [$R_F = CF_3(CF_2)_3$–], 20116-30-7; XII [$R_F = CF_3(CF_2)_2$–], 20116-31-8; XII amide [$R_F = CF_3(CF_2)_3$–], 20122-03-6; XIII [$R_F = CF_3(CF_2)_3$–], 20116-32-9; XIII ($R_F = CF_3CF_2CF_2$–), 20116-33-0; XIV ($R_F = CF_3CF_2CF_2$–), 20116-34-1; XVII ($R_F = CF_3CF_2CF_2CF_2$–), 20116-35-2; XIX ($R_F = CF_3CF_2CF_2$–), 20116-36-3; XX, 20122-02-5.

Acknowledgment.—Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to the U. S. Army Research Office (Durham) for partial support of this research.

Aqueous Fluorination of Carboxylic Acid Salts

V. GRAKAUSKAS

Environmental Systems Division, Aerojet-General Corporation, Azusa, California 91702

Received February 19, 1969

Direct fluorination of aqueous alkali salts of malonic, succinic, glutaric, adipic, azelaic, and sebacic acids proceeded with decarboxylation yielding ω-fluorocarboxylic acids and α,ω-difluoroalkanes. Monocarboxylic acids yielded 1-fluoroalkanes. Nonanoic acid, decanoic acid, and monomethyl adipate were used as substrates. 1-Fluoroalkanes and α,ω-difluoroalkanes underwent additional random fluorination. Fluorination of aqueous sodium *p*-nitrobenzoate gave *p*-fluoronitrobenzene. An ionic mechanism is proposed for these decarboxylative fluorination reactions.

As a part of a program on direct liquid phase fluorination of organic compounds in progress at this laboratory for the past several years, the fluorination of aqueous alkali salts of aliphatic carboxylic acids was investigated. The primary objective of this work was to extend the scope of liquid phase fluorination technique, previously applied in the fluorination of nitrogenous compounds,[1,2] nitronate salts,[3] aromatic compounds,[4,5] and aliphatic esters,[6] to other classes of organic compounds.

Electrochemical fluorination of short-chain carboxylic acids yields predominantly perfluoroalkanes,[7] but small amounts of the corresponding perfluoroacyl fluorides have also been obtained.[8] Carboxylic acids with six or more carbon atoms yield cyclic ethers as the major products.[9] The electrochemical fluorination of acyl halides to perfluoro acid fluorides is one of the most important applications of the electrochemical method. Dibasic acid fluorides, such as adipoyl and succinoyl, have been fluorinated in this manner to give dibasic perfluoro acid fluorides and monoacid fluorides.[8] The partial electrochemical fluorination of propionic and butyric acids was reported[10] to give mixtures of monofluoro derivatives in very low yields.

Very little work has been reported on direct fluorination of carboxylic acids. Bockemuller[11] obtained β- and γ-fluoro derivatives in the liquid phase fluorination of *n*-butyric acid, its anhydride, and chloride, and β-fluoroisobutyric acid in the fluorination of isobutyric acid. Bockemuller also investigated direct fluorination of acetic, succinic, and glutaric anhydrides, and acetic acid, in carbon tetrachloride, but found that all these substrates were unreactive. Miller and Prober[12] studied exhaustive fluorination of acetyl fluoride in the vapor phase at 100° and reported low yields of fluoroacetyl fluoride and difluoroacetyl fluoride. Liquid phase fluorination of acetic anhydride gave fluoroacetic acid and difluoroacetic acid.[6]

Fichter and Brunner,[13] whose work comes closest to the present study as far as the experimental technique is concerned, investigated the fluorination of aqueous potassium acetate in the presence of potassium carbonate and obtained methanol, formaldehyde, carbon dioxide, and ethylene. Fluorination of potassium propionate gave ethanol, acetaldehyde, and ethylene.

In the present work the fluorinations were conducted by passing fluorine diluted with nitrogen into aqueous solutions of alkali salts of carboxylic acids at 0–5° and, in some cases, at ambient temperatures. Thus, the fluorination of aqueous disodium adipate using 2 mol of fluorine at 0–5° was completed in 5 hr. The reaction proceeded smoothly and fluorine was well consumed. At the end of the reaction *ca.* 40% of the adipic acid was recovered. The major reaction product, obtained in 40% yield (23% conversion), was identified as 5-fluoropentanoic acid on the basis of its elemental analysis, nmr spectra (see Experimental Section for details), and the reported[14] physical properties for the compound. The acid was also esterified to the known methyl 5-fluoropentanoate.

A small amount of a volatile liquid obtained in the above experiment analyzed for approximately $C_4H_7F_3$. Its infrared spectrum showed a typical fluoroalkane structure, and gas chromatographic analysis indicated that the material was a mixture of several compounds. Based on the analytical data and its physical properties (bp 75–80°), the material appeared to be a mixture of randomly fluorinated butanes. The individual components were not isolated in this case, and it is possible that some of the more volatile fluorobutane isomers were lost during the process of fluorination.

Since the characterization of the fluoroalkane mixture obtained in the fluorination of disodium adipate presented some experimental problems, the fluorination of longer chain dicarboxylic acids was examined next with the primary objective of characterizing α,ω-difluoroalkanes. The fluorination of disodium sebacate using 2 mol of fluorine gave a liquid boiling in the range of fluorooctanes. The gas chromatographic analysis showed that this material was a mixture of at least five components. The compound present in the mixture at *ca.* 60% concentration was separated by gas chromatography and identified as 1,8-difluorooctane on the basis of elemental analysis and nmr spectra.

A small amount of a high-boiling liquid, isolated on further distillation of the crude reaction product, was identified as 9-fluorononanoic acid on the basis of reported[14] physical properties. The acid was also esterified to the known[14] ethyl 9-fluorononanoate. In this

(1) V. Grakauskas, Abstracts, the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 23M.

(2) V. Grakauskas, Third International Symposium on Fluorine Chemistry, Munich, Sept 1965.

(3) V. Grakauskas and K. Baum, *J. Org. Chem.*, **33**, 3080 (1968).

(4) V. Grakauskas, *ibid.*, in press.

(5) V. Grakauskas, Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967.

(6) V. Grakauskas, *J. Org. Chem.*, **34**, 963 (1969).

(7) For general discussion, see M. Stacey, J. C. Tatlow, and A. G. Sharpe, *Advan. Fluorine Chem.*, **1**, 145 (1960).

(8) H. M. Scholberg and H. G. Brice, U. S. Patent 2,717,871 (1955).

(9) C. F. Irwin, R. G. Brenner, A. F. Benning, F. B. Downing, H. M. Parmelee, and W. V. Wirtz, *Ind. Eng. Chem.*, **39**, 350 (1947).

(10) C. Slesser and S. R. Schram, Ed., "Preparation, Properties, and Technology of Fluorine and Organic Fluorine Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, p 485.

(11) W. Bockemuller, *Ann.*, **506**, 20 (1933).

(12) W. T. Miller and M. Prober, *J. Amer. Chem. Soc.*, **70**, 2602 (1948).

(13) F. Fichter and E. Brunner, *Helv. Chim. Acta*, **12**, 573 (1929).

(14) F. L. M. Pattison, S. B. D. Hunt, and J. B. Stothers, *J. Org. Chem.*, **21**, 883 (1950).

experiment *ca.* 50% of the sebacic acid was recovered. In another experiment using dipotassium sebacate and 3 mol of fluorine, a higher yield of fluorooctanes was obtained.

The relatively poor utilization of fluorine in the fluorination of adipic and sebacic acid salts, as well as in other cases to be discussed later, seems to be the result of a side reaction. The fluorination of aqueous sodium hydroxide is the standard method for preparing oxygen difluoride[15] and therefore it is not surprising that a significant portion of fluorine is consumed in the side reaction during the fluorination of aqueous alkali carboxylates. No attempts were made to determine the effect of pH of the fluorination mixture on the efficiency of fluorine utilization in decarboxylation reactions, but it seems reasonable to suspect that pH is the major reaction variable. Approximately half of the fluorine was utilized in the reaction with alkali carboxylates under the reaction conditions employed in this study.

The fluorination of several other dicarboxylic acids, azelaic, malonic, glutaric, and succinic, gave analogous results to those obtained with adipic and sebacic acids. Disodium azelate yielded a mixture of 1,7-difluoroheptane and randomly fluorinated 1,7-difluoroheptanes, analyzing for approximately $C_7H_{12.5}F_{2.5}$. 1,7-Difluoroheptane, the predominant component is this mixture, was isolated by gas chromatography and identified by nmr spectra. The monofluorination product was esterified and ethyl 8-fluorooctanoate was identified on the basis of reported[14] physical properties. The fluorination of disodium malonate gave fluoroacetic acid in *ca.* 1% yield, characterized by proton nmr spectrum, and also by comparing its properties with those reported[16] for the acid. The yield might have been distorted by the isolation technique: the fluorination was conducted in a dilute solution and it is possible that not all fluoroacetic acid was extracted.

The fluorination of potassium glutarate and potassium succinate gave 4-fluorobutyric and 3-fluoropropionic acids, respectively, in low yields. No attempts have been made in these cases to isolate α,ω-difluoroalkanes.

The fluorination of aqueous alkali salts of monocarboxylic acids was examined next, but some difficulties were encountered with the characterization of reaction products. 1-Fluoroalkanes, the products of these reactions, underwent random fluorination simultaneously with the fluorination of acids leading to a mixture of fluorocarbons. The unique proximity in boiling points of monofluoro and polyfluoro derivatives of an organic compound made the separation of such mixtures a difficult task.

The fluorination of aqueous sodium nonanoate yielded a liquid boiling in the range of fluorooctanes. Its infrared spectrum was typical of fluoroalkanes. The gas chromatographic analysis showed that the material was a mixture containing at least six components. The compound present in the mixture at the highest concentration (*ca.* 50%) was separated and identified as 1-fluorooctane on the basis of its elemental analysis and the proton nmr spectrum. The isolation and identification of other components in the mixture, presumably polyfluoro isomers of octane, could not be accomplished by gas chromatography because of very similar retention times.

The fluorination of aqueous potassium decanoate using 1 mol of fluorine proceeded analogously to that of nonanoate, yielding a mixture of fluorononanes analyzing for approximately $C_9H_{18.5}F_{1.5}$. The yield of fluoroalkanes in the above two reactions was low and large amounts of unreacted acids were recovered.

The fluorination of aqueous sodium methyl adipate using 1 mol of fluorine gave methyl 5-fluoropentanoate in 14% yield. The compound was identified by nmr

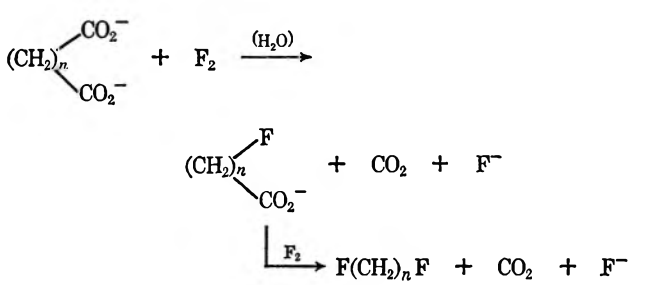
$$CH_3O_2C(CH_2)_4CO_2^- + F_2 \xrightarrow{(H_2O)} F(CH_2)_4CO_2CH_3 + F^- + CO_2$$

spectra and by comparing its properties with those reported[17] for the ester.

The fluorination of aqueous alkali salts of aromatic carboxylic acids was investigated briefly. No products could be isolated in the fluorination of sodium benzoate. The reaction mixture darkened considerably and some dark, viscous oil deposited. Recently it was shown that aromatic compounds undergo facile fluorination yielding addition[4] and substitution[5] products and it became apparent that fluorination in the aromatic nucleus would interfere with the decarboxylative fluorination of aromatic carboxylic acids. Although this conclusion seems to be generally correct, it appeared that the decarboxylative fluorination of electronegatively substituted aromatic carboxylic acids might compete, at least to a certain degree, with the fluorination in the aromatic nucleus which was shown to be the case. The fluorination of aqueous sodium *p*-nitrobenzoate gave *p*-fluoronitrobenzene in 4% yield, identified by fluorine analysis and infrared spectrum and by comparing its physical properties with those of *p*-fluoronitrobenzene. No attempts were made to identify other reaction products or to recover the unreacted *p*-nitrobenzoic acid.

In a few cases the fluorination of aqueous carboxylic acids was briefly investigated, but no indication of decarboxylative fluorination was noticed. The fluorine was apparently consumed in random fluorination of the hydrocarbon chains of the acids as observed by Bochemuller.[11]

The results of aqueous fluorination of adipic and sebacic acids salts showed that dicarboxylic acids underwent stepwise fluorination by decarboxylation and yielded ω-fluorocarboxylic acids and γ,ω-difluoroalkanes. The water-insoluble γ,ω-difluoroalkanes underwent additional random fluorination leading to mixtures of polyfluoroalkanes. The fact that the recovered



(15) D. M. Yost, "Inorganic Synthesis," Vol. I, H. S. Booth, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p 109.

(16) B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 1773 (1948).

(17) F. L. M. Pattison, *J. Amer. Chem. Soc.*, **78**, 2255 (1956).

starting material and ω-fluorocarboxylic acids were not randomly fluorinated indicated that random fluorination occurred after α,ω-difluoroalkanes were produced. Apparently, α,ω-difluoroalkanes solubilize fluorine better than water, and a higher concentration of fluorine in the organic phase provides favorable conditions for random fluorination. It would appear that random fluorination could be suppressed by a variety of means, for example, by removing α,ω-difluoroalkanes as they are produced, either mechanically or by extraction, but this was not attempted in the present work.

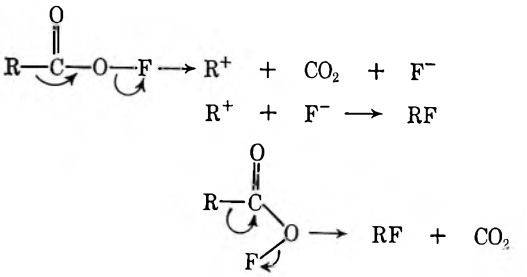
The observation that little, if any, random fluorination occurs in the aqueous phase also indicates that fluorine reacts at a much faster rate with the carboxylate anion than with the hydrocarbon chain of an acid.

Aqueous fluorination of alkali carboxylates can be looked upon as a special case of the Hunsdieker reaction.[18] Although the reaction conditions differ greatly, the fluorination of aqueous alkali salts and the bromination of dry silver salts of carboxylic acids proceed by the loss of carbon dioxide yielding 1-haloalkanes in the case of monobasic acids, or α,ω-dihaloalkanes when dibasic carboxylic acids are used. It is generally agreed that the initial step in the Hunsdieker reaction involves the formation of acyl hypobromite intermediates, but there is no general agreement regarding the subsequent steps of the mechanism.[19] A free-radical mechanism is favored by most investigators, but some arguments have been present for an ionic mechanism.[20-23]

Aqueous fluorination of alkali carboxylates most likely also proceeds *via* acyl hypofluorite intermediates. Whereas only indirect evidence exists for acyl hypobromites, several acyl hypofluorites have actually been isolated. Cady and coworkers obtained trifluoroacetyl hypofluorite in the vapor phase fluorination of trifluoroacetic acid[24] and showed[25] that the compound decomposes into carbon dioxide and tetrafluoromethane by a free-radical mechanism. Pentafluoropropionyl hypofluorite, synthesized by Steward and Cady[26] in a similar manner, decomposed into hexafluoroethane and carbon dioxide. Although both free-radical and ionic mechanisms might be considered in the aqueous fluorination of carboxylic acid salts, we favor the latter primarily because of a strongly polar medium in which these reactions were conducted. The relative insta-

$$RCO_2^-Na^+ + F_2 \xrightarrow{(H_2O)} [RCO_2F] + NaF$$

bility of perfluoroacly hypofluorites observed by Cady suggest that acyl hypofluorites are even less stable and decompose into alkyl fluorides and carbon dioxide. An ionic solvent-cage mechanism or SNi decomposition mechanism would be expected to be favored in a polar medium.



The decomposition of acyl hypofluorites by a free-radical mechanism, analogous to that proposed by Cady for the decomposition of perfluoroacyl hypofluorites, cannot be eliminated but seems to be less likely under the present reaction conditions. It would appear that a free-radical decomposition of acyl hypofluorites would have resulted in side reaction products not detected in the present work. Thus, Stump, Oliver, and Podgeti[27] reported that the decarboxylation of nitrite esters of perfluorosuccinic acid and perfluoroglutaric acid, either by pyrolysis or ultraviolet irradiation, gave large amounts of by-products arising from free-radical side reactions.

Similarities and differences between aqueous fluorination of carboxylic acids salts and the Hunsdieker reaction might be rationalized as follows. In aqueous solution, fluorine reacts with carboxylic acid anions to give acyl hypofluorites. Under similar conditions, chlorine or bromine either do not react at all with carboxylic acid anions or if the acyl hypohalite intermediates are formed they decompose to carboxylic acids as it is in the case when moisture is present in the Hunsdieker reaction. Cady's finding that trifluoroacetyl hypofluorite is stable in the presence of water[24] suggests that acyl hypofluorites produced in aqueous fluorination reactions are not decomposed by water but rather undergo decarboxylation reactions in a similar manner as do acyl hypochlorites or acyl hypobromites under anhydrous reaction conditions.

Experimental Section

General.—Fluorinations were carried out in a glass, standard taper, three-necked flasks fitted with a mechanical stirrer, a glass tube extending below the liquid level used as a gas inlet, and a standard taper thermometer well with an opening for gas exit. Standard fluorine-handling hardware[28] was used and the fluorine was diluted with nitrogen (1:3 to 1:6 ratio). Safety shielding is strongly recommended.[29]

Fluorination of Disodium Adipate.—A solution of 292.2 g (2.0 mol) of adipic acid in 3500 ml of water containing 160 g (4.0 mol) of sodium hydroxide was fluorinated at 0–5° until 4 mol of fluorine was consumed (5 hr). The fluorination mixture containing *ca.* 5–10 ml of water-insoluble liquid was acidified with 50% sulfuric acid. A white solid which precipitated on acidification was filtered, washed with three 200-ml portions of methylene chloride, and dried in the air: weight 120 g; mp 150–153°, alone, or when mixed with an authentic sample of adipic acid.

The methylene chloride washings were used to extract the aqueous filtrate. The extract was dried, filtered, and the filtrate was distilled to give 55 g of a colorless liquid: bp 57–58° (0.1 mm); $n^{25}D$ 1.4090; identified as 5-fluoropentanoic acid [lit.[14] bp 90° (4 mm); $n^{25}D$ 1.4078, 1.4080]; yield 40% (23% conversion).

(18) For a general review on the Hunsdieker reaction, see: (a) R. G. Johnson and R. K. Ingham, *Chem. Rev.*, **56**, 219 (1956); (b) Houben-Weyl, "Methoden der organischen Chemie," E. Muller, Ed., Vol. V/4, 4th ed, Georg Thieme Verlag, Stuttgart, 1960, pp 488–500.

(19) W. E. Doering and M. Farber, *J. Amer. Chem. Soc.*, **71**, 1514 (1949); J. W. Wilt, *ibid.*, **77**, 6397 (1955).

(20) M. Rottenberg, *Experientia*, **7**, 432 (1951).

(21) G. Darzens and M. Meyer, *C. R. Acad. Sci., Paris*, **237**, 1334 (1953).

(22) K. B. Wiberg and T. M. Shryne, *J. Amer. Chem. Soc.*, **77**, 2774 1955).

(23) S. L. Levitt and E. R. Malinvski, *ibid.*, **77**, 4517 (1955).

(24) G. H. Cady and K. B. Kellog, *ibid.*, **75**, 2501 (1953).

(25) R. D. Steward and G. H. Cady, *ibid.*, **77**, 6110 (1955).

(26) A. Menefee and G. H. Cady, *ibid.*, **76**, 2020 (1954).

(27) E. C. Stump, W. H. Oliver, and C. D. Padgeti, *J. Org. Chem.*, **33**, 2102 (1958).

(28) Allied Chemical Corp., Data Sheet PD-TA-84513A.

(29) Although no problems were encountered in the present work, direct fluorination of organic compounds must be considered a potentially dangerous operation and adequate safety precautions should be exercised.

Anal. Calcd for $C_5H_9FO_2$: C, 50.0; H, 7.55; F, 15.8. Found: C, 50.2; H, 7.1; F, 15.4.

The fluorine nmr spectrum exhibited one signal at ϕ 219.5, a triplet, $J_{HF_{gem}}$ = 47.1 cps, of triplets, $J_{HF_{vic}}$ = 25.9 cps (superposition of triplets made the signal appear as a symmetrical quintet), with additional fine 1–3 H–F splitting. The proton nmr spectrum exhibited five signals: a singlet at δ 11.70 was assigned to the carboxylic proton; a doublet, J_{HF} = 47.6 cps of triplets, $J_{H-H} \cong$ 5.5 cps, at δ 4.44 to the FCH_2 protons; a triplet at δ 2.41 to the $-CH_2CO_2H$ protons; and two partially superimposed complex multiplets centering at δ 1.62 and 1.87 to the protons of β and γ methylene groups. The area ratio of the signals was approximately 1:2:2:2:2.

Redistillation of methylene chloride removed in the isolation of the acid yielded 7.5 g of a colorless liquid, bp 75–80°. The infrared spectrum showed bands at 3.4 (m), 3.5 (m), 6.83 (w), 7.21 (m), and a broad absorption envelope at 8.9–9.7 μ.

Anal. Calcd for $C_4H_7F_3$: C, 42.9; H, 6.2; F, 50.9. Found: C, 41.8; H, 5.8; F, 51.8.

Methyl 5-Fluoropentanoate.—To a solution of 6.0 g of 5-fluoropentanoic acid above in 50 ml of methanol was added 2 drops of concentrated sulfuric acid and the mixture was refluxed for 5 hr. The solution was cooled to 10°, added to 200 ml of ice water, and extracted with three 50-ml portions of methylene chloride. The combined extracts were distilled to give 5.5 g of methyl 5-fluoropentanoate: bp 62–63° (18 mm); $n^{25}D$ 1.3975 [lit.[17] bp 72–74° (25 mm); $n^{25}D$ 1.3973].

Fluorination of Sodium Methyl Adipate.—A solution of 80 g (0.5 mol) of monomethyl adipate in 750 ml of water containing 20 g (0.5 mol) of sodium hydroxide was fluorinated at 3–5° until 0.5 mol of fluorine was consumed. The fluorination mixture was made basic by adding 15 g of sodium hydroxide and the resulting solution was extracted with 100 ml of methylene chloride. The extract was distilled to give 19 g of a colorless liquid: bp 74–75° (25 mm); $n^{25}D$ 1.3979; identified as methyl 5-fluoropentanoate[11] [lit.[14] bp 72–74° (25 mm); $n^{25}D$ 1.3973]; yield 14.2%.

The fluorine nmr spectrum in carbon tetrachloride exhibited a triplet, $J_{HF_{gem}}$ = 47.5 cps, of triplets, $J_{HF_{vic}}$ = 25.7 cps, at ϕ 219.5. The proton nmr spectrum exhibited five signals: a doublet, J_{HF} = 47.4 cps, of triplets, $J_{HH} \cong$ 5.5 cps, assigned to the FCH_2 protons; a singlet at δ 3.68, to the OCH_3 proton of the ester group; a triplet of δ 2.38, to the $-CH_2CO_2-$ protons; and two partially overlapping multiplets centered at δ 1.62 and δ 1.87, to the protons of β and γ methylenes. The area ratio of the above signals was 2:3:2:2:2. A very weak doublet of δ 5.70, $J_{HF} \cong$ 51 cps, was assigned to the $-CO_2CH_2F$ protons of fluoromethyl 5-fluoropentanoate, present as an impurity, on the basis of reported[6] proton nmr spectrum of fluoromethyl esters.

Fluorination of Disodium Sebacate.—A solution of 101 g (0.5 mol) of sebacic acid in 1500 ml of water containing 42 g (1.05 mol) of sodium hydroxide was fluorinated at 10 ± 5° until 1 mol of fluorine was consumed (3.5 hr). The fluorination mixture was made basic with 100 ml of 50% aqueous sodium hydroxide and extracted with three 100-ml portions of diethyl ether. The combined ether extracts were distilled to give 22 g of a colorless liquid: bp 34–36° (0.2 mm); $n^{25}D$ 1.3885 (lit.[30] for 1,8-difluorooctane, $n^{25}D$ 1.3933).

Anal. Calcd for $C_8H_{15}F_3$: C, 57.1; H, 8.8; F, 33.9. Found: C, 57.1; H, 8.7; F, 33.9.

The proton nmr spectrum in carbon tetrachloride exhibited a very intense broad signal centered at δ 1.6, a weak complex multiplet at δ 1.67, and two complex multiplets of equal area at δ 4.0 and 4.75. The chemical shift and the structure of the latter two multiplets suggested that they represented several superimposed doublets of triplets of FCH_2 groups. The fluorine nmr spectrum exhibited six complex multiplets at ϕ 116.2, 182.6, 185.0, 189.7, 219.5, 222.1, and 230.9, the most intense of which at ϕ 219.5, an overlapping triplet, $J_{HF_{gem}}$ = 47.6 cps, of triplets, $J_{HF_{vic}} \cong$ 24 cps, was assigned to the terminal FCH_2 fluorines of 1,8-difluorooctane based on analogy with the fluorine nmr spectra of 5-fluoropentanoic acid and methyl 5-fluoropentanoate (see above). The infrared spectrum indicated a typical fluoroalkane structure.

Gas chromatographic analysis using 24 ft × 1/4 in. column of 10% Carbowax 4000 on Fluoropak 80, 95°, He flow rate 50 cc/min, showed that the mixture at *ca.* 60% concentration was separated (retention time 42 min) and identified as 1,8-difluorooctane.

Anal. Calcd for $C_8H_{16}F_2$: C, 63.96; H, 10.74; F, 25.30. Found: C, 63.4; H, 10.4; F, 25.4.

The proton nmr spectrum (in microcell) exhibited a doublet, J_{HF} = 47.7 cps, of triplets at δ 4.35 assigned to the FCH_2 protons (the high-field triplet was broadened). A poorly resolved multiplet at δ 1.85 was assigned to the FCH_2CH_2- methylene protons, and a broadened signal at δ 1.39 to the remaining protons in the chain. The area ratio of the signals agreed well with the required 1:1:2.

The alkaline aqueous phase was acidified with 50% aqueous sulfuric acid. A white solid which precipitated on acidification was filtered, washed with three 100-ml portions of diethyl ether, and dried in air: weight 48.5 g; mp 133–135°, alone or when mixed with an authentic sample of sebacic acid. The filtrate was extracted with four 100-ml portions of diethyl ether. The etheral extracts, combined with the ether washings above, were distilled to give 3.5 g of a colorless liquid, bp 102–104° (0.2 mm), $n^{25}D$ 1.4285, which was identified as 9-fluorononanoic acid on the basis of the reported[14] boiling point, 100–101° (0.15 mm), and refractive index, $n^{25}D$ 1.4289, for the compound.

9-Fluorononanoic acid above, 2.5 g, was dissolved in 10 ml of absolute ethanol. 1 drop of concentrated sulfuric acid added, and the mixture was refluxed for 4.0 hr. The solution was cooled, added to 50 g of crushed ice, and the resulting mixture was extracted with 15 ml of methylene chloride. The extract was distilled to give 2.5 g of colorless liquid: bp 76–78° (0.2 mm); $n^{25}D$ 1.4190. The compound was identified as ethyl 9-fluorononanoate on the basis of the reported[14] boiling point, 87–88° (1 mm), and refractive index, 1.4191, for the ester.

In another experiment, a solution of 162 g (0.8 mol) of sebacic acid in 1500 ml of water containing 132 g of 85% potassium hydroxide (2.0 mol of KOH) was fluorinated at 25–30° until 1.5 mol of fluorine was consumed. At this stage, the fluorination was interrupted, another 1.0 mol of potassium hydroxide added to the reaction mixture, and the fluorination was resumed and continued until an additional 1.0 mol of fluorine was consumed. The pH of the reaction mixture at the end of fluorination was 6–7, and a large amount of water-insoluble heavy liquid was present. The mixture was acidified with 50% sulfuric acid to pH 1–2, and extracted with three 200-ml portions of methylene chloride. The combined extracts were distilled to give (1) 91 g of colorless liquid, bp 33–36° (0.2 mm); (2) 20 g of slightly dark liquid, bp 101–105° (0.1 mm); and (3) dark, viscous distillation residue amounting to 20 g.

Anal. of fraction 1. Calcd for $C_8H_{15}F_3$: C, 57.1; H, 8.8; F, 33.9. Found: C, 55.6; H, 8.2; F, 34.8.

The proton and fluorine nmr spectra were identical with those above, with the exception that the ϕ 116.4 signal in the fluorine spectrum was resolved into a doublet, $J_{HF_{gem}}$ = 56.8 cps, of triplets, $J_{HF_{vic}}$ = 16.6 cps, suggesting the presence of $-CHF_2$ groups.

The material of fraction 2 above was esterified with ethanol yielding 12.5 g of ethyl 9-fluorononanoate: bp 76–79° (0.2 mm); $n^{25}D$ 1.4190.

The distillation residue (3) was not characterized, but probably contained mainly unreacted sebacic acid. The material crystallized at room temperature.

Fluorination of Disodium Azelate.—A solution of 376.5 g (2.0 mol) of azelaic acid in 3500 ml of water containing 160 g (4.0 mol) of sodium hydroxide was fluorinated at 5° until 3.0 mol of fluorine was consumed (3.0 hr). The fluorination mixture was acidified with 200 g of concentrated sulfuric acid and filtered. The filter cake was washed with two 250-ml portions of methylene chloride and the white solid was dried: weight 150 g; mp 105–106°, alone or when mixed with an authentic sample of azelaic acid. The aqueous filtrate was extracted with two 400-ml portions of methylene chloride, the extracts were combined with the methylene chloride washings above, and the combined solution was distilled to give 60 g of a colorless liquid, bp 30–35° (0.2 mm). The material was redistilled to give (1) 4.5 g of colorless liquid, bp 23–25° (0.5 mm), and (2) 55 g of colorless liquid, bp 32–33° (0.1 mm).

Anal. of fraction 1. Calcd for $C_7H_{12}F_4$: C, 48.8; H, 7.0; F, 44.2. Found: C, 48.0; H, 6.8; F, 45.0.

Anal. of fraction 2. Calcd for $C_7H_{14}F_2$: C, 61.7; H, 10.4; F, 29.9. Calcd for $C_7H_{13}F_3$: C, 54.5; H, 8.5; F, 37.0. Found: C, 56.8; H, 9.2; F, 31.2.

(30) F. L. M. Pattison and R. G. Woolford, *J. Amer. Chem. Soc.*, **79**, 2308 (1957).

The proton nmr spectrum of fraction 2 exhibited five broadened, partially superimposed complex multiplets centered at approximately δ 4.4, 3.6, 2.3, 1.8, and 1.4. The δ 4.4 and δ 3.6 multiplets, equal in area, seem to represent the FCH_2– protons of several α-fluoroalkanes, $J_{HF_{gem}} = 47$ cps.

The distillation residue amounting to *ca.* 100 g, bp > 80° (0.1 mm), was dissolved in 250 ml of methanol, 2 drops of concentrated sulfuric acid added, and the resulting solution was refluxed for 6 hr. The mixture was cooled, added to 1200 ml of ice water, and extracted with 100 ml of methylene chloride. The extract was distilled to give 65 g of colorless liquid, bp 59–61° (0.1 mm), identified as methyl 8-fluorooctanoate on the basis of the reported[14] boiling point, 106.5–107° (9 mm), for the ester.

Anal. Calcd for $C_9H_{17}FO_2$: C, 61.3; H, 9.7; F, 10.8. Found: C, 60.9; H, 9.4; F, 11.4.

The proton nmr spectrum exhibited five signals. A doublet, $J_{HF} = 47.7$ cps, of triplets, $J_{HH} \cong 5.5$ cps, at 4.34 was assigned to the FCH_2 protons; a singlet of δ 3.64 to the $-OCH_3$ protons of the ester group; a triplet at δ 2.29 to the $-CH_2CO_2-$ protons; a poorly resolved multiplet at δ 1.75 to the $-CH_2CH_2CO_2-$ protons; and an intense broad signal centered at δ 1.38 to the protons of the internal methylene groups. The area ratio of the signals was approximately 2:3:2:2:8. The fluorine nmr spectrum exhibited a single signal, a triplet, $J_{HF_{gem}} = 48$ cps, of triplets, $J_{HF_{vic}} \cong 24$ cps, at ϕ 218.7. Additional fine splitting due to 1,3 H–F coupling was visible.

In another experiment, a solution of 94 g (0.5 mol) of azelaic acid in 1500 ml of water containing 44 g (1.1 mol) of sodium hydroxide was fluorinated at 0–5° until 1.1 mol of fluorine was consumed (2.5 hr) (very smooth fluorination); pH of reaction mixture at the end of the run was 5–6. The reaction mixture was extracted with two 150-ml portions of methylene chloride and the combined extracts were distilled to give 32 g of a colorless liquid, bp 33–35° (0.2 mm).

Anal. Found: C, 53.5; H, 7.8; F, 33.0.

Gas chromatographic analysis indicated that the material contained at least six components. The most predominant compound present in the mixture, 1,7-difluoroheptane, was separated by gas chromatography.

Anal. Calcd for $C_7H_{14}F_2$: C, 61.73; H, 10.36; F, 27.90. Found: C, 60.9; H, 9.7; F, 28.5.

The proton nmr spectrum exhibited three signals. A doublet, $J_{HF} = 47.3$ cps, of triplets, $J_{HF} \cong 5.6$ cps, at δ 4.46 assigned to the FCH_2 protons, a complex multiplet centered at δ 1.88, assigned to the FCH_2CH_2- protons, a broad signal centered at δ 1.40, assigned to the protons of the three remaining methylene groups. The area ratio of the three signals was approximately 2:2:3.

On further distillation the crude reaction product yielded 35 g of a colorless liquid, bp 85–88° (0.05 mm), which partially solidified to a white crystalline solid at room temperature. The material was identified as 8-fluorooctanoic acid on the basis of reported[14] physical properties: bp 145–148° (10 mm); mp 34–35°.

Anal. Calcd for $C_8H_{15}FO_2$: C, 59.2; H, 9.3; F, 11.7. Found: C, 58.6; H, 8.7; F, 13.5.

Fluorination of Disodium Malonate.—A solution of 208 g (2.0 mol) of malonic acid in 1600 ml of water containing 160 g (4.0 mol) of sodium hydroxide was fluorinated at 0–5° until 2.0 mol of fluorine was consumed. The solution was acidified with 50% sulfuric acid and extracted with six 100-ml portions of diethyl ether. The combined ether extracts were dried, filtered, and the filtrate was distilled to give 2.2 g of a colorless liquid, bp 37–39° (0.2 mm), $n^{25}D$ 1.3800, which solidified at room temperature. The differential thermal analysis showed an endotherm of 166°, indicating that this was the boiling point of the compound. The compound was identified as fluoroacetic acid on the basis of reported[16] physical properties, bp 167–168.5, mp 31–32°, for the acid.

The proton nmr spectrum in water exhibited a doublet, $J_{HF} = 47$ cps, at δ 5.00. Sodium 2,2-dimethyl-2-silapentane-5-sulfonate (SDSS) was used as internal reference.

4-Fluorobutyric Acid.—A solution of 33 g (0.25 mol) of glutaric acid in 450 ml of water containing 40 g of 85% potassium hydroxide (0.6 mol of KOH) was fluorinated at 10° until 0.3 mol of fluorine was consumed. The fluorination mixture was acidified with 50% sulfuric acid, extracted with three 100-ml portions of methylene chloride, and the combined extracts were distilled to give 4.5 g of 4-fluorobutyric acid: bp 62–63° (3 mm); $n^{25}D$ 1.4010 [lit.[14] bp 60–62° (2 mm)].

3-Fluoropropionic Acid.—A solution of 23.6 g (0.2 mol) of succinic acid in 450 ml of water containing 0.5 mol of potassium hydroxide was fluorinated and the reaction product isolated as above to give 2.1 g of 3-fluoropropionic acid: bp 100–101° (25 mm); $n^{25}D$ 1.3884 [lit.[14] bp 97° (29 mm); $n^{25}D$ 1.3888].

Fluorination of Sodium Nonanoate.—A solution of 79 g (0.5 mol) of nonanoic acid in 1400 ml of water containing 22 g (0.55 mol) of sodium hydroxide was fluorinated at 0–5° until 0.5 mol of fluorine was consumed (3.0 hr). The reaction mixture was extracted with two 150-ml portions of methylene chloride and the combined extracts were distilled to give 18 g of a colorless liquid, bp 50–60° (25 mm). Gas chromatographic analysis indicated that the material was a mixture of at least six components. The predominant component present in the mixture to the extent of *ca.* 50% was separated by gas chromatography and identified as 1-fluorooctane.

Anal. Calcd for $C_8H_{17}F$: C, 72.7; H, 13.0; F, 14.4. Found: C, 71.7; H, 12.6; F, 14.4.

The proton nmr spectrum exhibited a doublet, $J_{HF_{gem}} = 47.5$ cps, of triplets, $J_{HH_{vic}} \cong 5.6$ cps, at δ 4.38 assigned to the FCH_2– protons; a broad poorly resolved multiplet centered at δ 1.9 and an intense broad signal at δ 1.37 were assigned to the protons of the other six methylene groups; and a poorly resolved triplet at δ 0.88, assigned to the protons of the CH_3 group. The approximate area ratio of FCH_2–, $-CH_2-$, and $-CH_3$ signals was the required 2:12:3.

The aqueous solution was acidified with 50% sulfuric acid, extracted with four 150-ml portions of diethyl ether, and the combined extracts were distilled to give 51 g of colorless liquid, bp 85–86° (0.1 mm), which was identified as the starting material (65% recovery) by comparing its infrared spectrum with that of nonanoic acid. Elemental analysis indicated no fluorine.

Fluorination of Potassium Decanoate.—A solution of 43 g (0.25 mol) of decanoic acid in 350 ml of water containing 0.3 mol of potassium hydroxide was fluorinated at 15–20° until 0.25 mol of fluorine was consumed. At this stage, the fluorination was interrupted, another 0.2 mol of potassium hydroxide was added to the solution, and the fluorination was resumed and continued until another 0.25 mol of fluorine was consumed. Total fluorination time was 3.5 hr. The reaction mixture was made basic with 50% aqueous potassium hydroxide and extracted with 75 ml of methylene chloride. The extract was distilled to give 19 g of a colorless liquid: bp 30–40° (0.3 mm); $n^{25}D$ 1.4015.

Anal. Calcd for $C_9H_{19}F$: C, 74.0; H, 13.0; F, 13.0. Calcd for $C_3H_{18}F_2$: C, 65.8; H, 11.0; F, 23.2. Found: C, 67.8; H, 12.2; F, 19.7.

The infrared spectrum was typical for fluoroalkanes: at 3.4 and 3.5 μ, aliphatic CH stretching; at 6.85 and 7.23 μ, $-CH_2$ and CH_3 deformations; a broad absorption envelope with peaks at 8.9, 9.5, and 9.9 μ indicated CF bonding.

Fluorination of Sodium *p*-Nitrobenzoate.—A solution of 167.1 g (1.0 mol) of *p*-nitrobenzoic acid in 1200 ml of water containing 44 g (1.1 mol) of sodium hydroxide was fluorinated at 0–5° until *ca.* 0.5 mol of fluorine was consumed. The fluorination mixture was made strongly alkaline with 20 g (0.5 mol) of sodium hydroxide and the resulting solution was extracted with two 150-ml portions of methylene chloride. The combined extracts were distilled to give 2.8 g of *p*-fluoronitrobenzene: bp 202–204°; $n^{25}D$ 1.5350 (lit.[31,32] bp 203–204°; $n^{25}D$ 1.5340.

Anal. Calcd for $C_6H_4NFO_2$: F, 13.5. Found: F, 14.1.

The infrared spectrum was identical with that of an authentic sample of *p*-fluoronitrobenzene.

Registry No.—Disodium adipate, 7486-38-6; sodium methyl adipate, 5877-45-2; disodium sebacate, 17265-14-4; disodium azelate, 17265-13-3; disodium malonate 141-95-7; sodium nonanoate, 14047-60-0; potassium decanoate, 13040-18-1; sodium *p*-nitrobenzoate, 3847-57-2.

Acknowledgment.—The author wishes to thank Mr. K. Inouye for the elemental analysis, Dr. H. M. Nelson for the nmr spectra, and Dr. K. Baum for useful discussions and help with the manuscript.

(31) G. C. Finger and C. W. Kruse, *J. Amer. Chem. Soc.*, **78**, 6034 (1956).

(32) N. N. Vorozhtsov and G. G. Yakobson, *Khim. Nauka i Promy.*, **3**, 403 (1958).

Bis- and Tris(difluoramino)alkanes. Beckmann Rearrangement and Fragmentation of α-Difluoraminofluorimines

TRAVIS E. STEVENS

Rohm and Haas Company, Redstone Research Laboratories, Huntsville, Alabama 35807

Received February 11, 1969

α-Substituted α-difluoraminofluorimines and α,α-bis(difluoramino)fluorimines undergo Beckmann fragmentations and rearrangements. Fragmentation in the presence of boron trifluoride produces α-substituted α-difluoramino fluorides; in the presence of difluoramine, 1,1-bis- and 1,1,1-tris(difluoramino)alkanes are formed. Rearrangement, however, is the major reaction path for α,α-bis(difluoramino)fluorimines, and a variety of products, including the expected amides, are produced. Characterization of the Beckmann products and the possible pathways leading to them are discussed in detail.

A variety of methods for preparing polydifluoramino compounds have evolved in the last decade. Among these methods are the addition of tetrafluorohydrazine (N_2F_4) to olefins,[1] the reaction of difluoramine (HNF_2) and carbonyl compounds to give geminal bis(difluoramino)alkanes,[2] the preparation of 1,2,2-tris(difluoramino)alkanes by a combination of the N_2F_4 and HNF_2 reactions,[3] and routes centered on additions to perfluoroguanidines.[4]

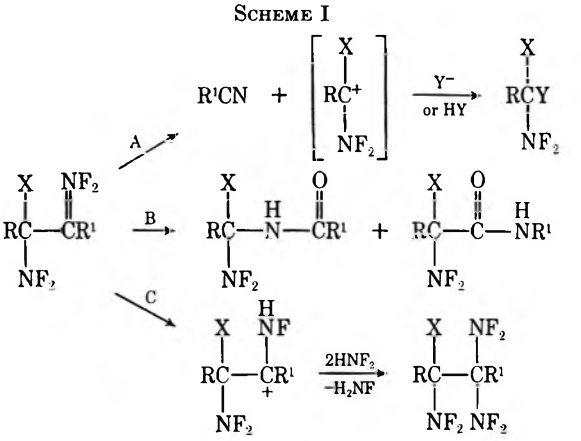
The addition of alcohols to perfluoroguanidine, followed by fluorination of the adduct,[4] provided a great variety of α,α,α-tris(difluoramino) ethers, but no general route to 1,1,1-tris(difluoramino)alkanes or 1-halo-1,1-bis(difluoramino)alkanes has been developed. For the reasons outlined earlier,[2] addition of HNF_2 to acid halides, esters, or ortho esters did not give such difluoramines.

To prepare bis- and tris(difluoramino)alkanes by alkylation of difluoramine, a convenient source of α-difluoramino- and α,α-bis(difluoramino)carbonium ions was necessary. When it was discovered that α-difluoraminofluorimines would cleave under acidic conditions (path A), in a process obviously related to the well-known Beckmann fragmentation,[5] a source of such carbonium ions for alkylation of difluoramine was available.

Other reaction paths are possible when molecules such as α-difluoraminofluorimines are treated with strong acid. The usual Beckmann rearrangement (Scheme I, path B) is shown, as well as one involving protonation on nitrogen (path C). The latter might eventually lead to a tris- or tetrakis(difluoramino)-alkane, but no evidence for path C was found in this work. Loss of fluoride ion from the difluoramino group, accompanied by migration of hydrogen or alkyl group, is also a known reaction of difluoramines.[6,7]

This paper summarizes a study of the Beckmann fragmentation and rearrangement reactions of a variety of α-substituted α-difluoramino- and α,α-bis(difluoramino)fluorimines, and reports a general route to

SCHEME I



geminal bis(difluoramines) and 1,1,1-tris(difluoramino)-alkanes that are not readily accessible by other synthetic routes.

The structures of some of the materials used in this study are summarized in Table I; they provide the key to Tables II–V.

Preparation of Fluorimines.—A tabulation of the unreported fluorimines used in this study is given in Table II. The α-substituted α-difluoraminofluorimines were readily prepared by addition of tetrafluorohydrazine to the appropriate olefin,[1] followed by dehydrofluorination with alcoholic base or an amine. Dehydrofluorination of α,α,β-tris(difluoramino) materials[3] provided the samples of α,α-bis(difluoramino)-fluorimines.

The fluorimine function, when an α C–H bond is available, will undergo a Neber reaction.[8] Thus, it was best to avoid an excess of a strong base such as methoxide when conducting dehydrofluorinations.

All the fluorimines reported in Table II were, according to their ^{19}F nmr spectra, of only one configuration. Presumably the fluorine of the fluorimine function is oriented *trans* to the α-difluoramino group.

Reactions of α-Substituted α-Difluoraminofluorimines.—Admittedly, most of our interest in the chemistry of fluorimines was centered on a synthetic route to the 1,1,1-tris(difluoramino)alkanes. Certain α-substituted α-difluoraminofluorimines were examined, however, not only to gain a better understanding of the reaction but also with the hope that certain fluorimines, such as α-halo materials, would directly produce the tris(difluoramino)alkanes when exposed to

(1) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967).

(2) (a) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083, 7089 (1968); (b) W. H. Graham and J. P. Freeman, *J. Org. Chem.*, in press.

(3) J. P. Freeman, R. C. Petry, and T. E. Stevens, *J. Amer. Chem. Soc.*, in press.

(4) (a) R. A. Davis, J. L. Koon, and D. A. Rausch, *J. Org. Chem.*, **32**, 1662 (1967); (b) R. L. Rebertus and P. F. Toren, *ibid.*, **32**, 4045 (1967).

(5) Reviewed by P. A. S. Smith, "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1964, pp 483–507.

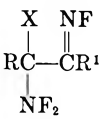
(6) K. Baum and H. M. Nelson, *J. Amer. Chem. Soc.*, **88**, 4459 (1966); T. E. Stevens and W. H. Graham, *ibid.*, **89**, 182 (1967).

(7) T. E. Stevens, *Chem. Commun.*, 1181 (1967).

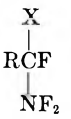
(8) W. H. Graham and T. E. Stevens, unpublished results.

TABLE I

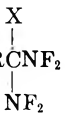
STRUCTURES OF FLUORAMINES



No.	R	R¹	X
1	CH_3	CH_3	CH_3
2	C_6H_5	CH_3	CH_3
3	CH_3	C_6H_5	CH_3
4	CH_3	CH_3	Cl
5	CH_3	CH_3	Br
6	4-BrC_6H_4	CH_3	Cl
7	CH_3	CH_3	NF_2
8	$-(CH_2)_4-$		CH_3
9	$-(CH_2)_3-$		NF_2
10	$-(CH_2)_4-$		NF_2
11	$-(CH_2)_5-$		NF_2
12	C_6H_5	C_2H_5	NF_2
13	4-ClC_6H_4	CH_3	NF_2
14	4-$CH_3OC_6H_4$	CH_3	NF_2
15	4-BrC_6H_4	CH_3	NF_2
16	C_6H_5	CH_3	Cl
17	C_6H_5	CH_3	Br
18	$-(CH_2)_4-$		Cl
25	C_6H_5	C_6H_5	F
34	CH_3	C_6H_5	NF_2
35	C_6H_5	CH_3	NF_2



No.	R	X
19	C_6H_5	Cl
20	C_6H_5	Br
21	C_6H_5	CH_3
22	$-(CH_2)_4CN$	Cl
23	$-(CH_2)_4CN$	CH_3
24	$-(CH_2)_3CN$	NF_2



No.	R	X
26	CH_3	Cl
27	C_6H_5	Cl
28	C_6H_5	Br
29	C_6H_5	F
30	$-(CH_2)_4CN$	Cl
31	$-(CH_2)_4CN$	CH_3
32	4-BrC_6H_4	Cl
36	C_6H_5	NF_2
37a	4-$CH_3OC_6H_4$	NF_2
37b	4-ClC_6H_4	NF_2
38	$-(CH_2)_3CN$	NF_2
39	$-(CH_2)_4CN$	NF_2
40	$-(CH_2)_5CN$	NF_2

TABLE II

α-DIFLUORAMINOFLUORIMINES

Fluorimine	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	^{19}F nmr spectra[a] $-NF_2$, ϕ[a]	^{19}F nmr spectra[a] $-NF$, ϕ[a]
1[b]	38.96	5.88	18.18	39.28	6.23	18.43	−27.4	−27.7
2	55.55	5.13	12.96	55.35	5.27	13.45	F_A −30.0	
							F_B −25.0	−28.5
							J_{FF} = 580	
3[c]	55.55	5.13	12.96	55.30	5.38	12.62	−29.5	−38.6
4[d]	27.52	3.47	16.05	28.05	3.72	15.49	F_A −40.9	
							F_B −29.5	−34.6
							J_{FF} = 580	
5	21.93	2.76	12.79	22.13	2.86	12.71	F_A −48.6	
							F_B −32.2	−34.4
							J_{FF} = 568	
6	34.25	2.24	8.80	33.71	2.61	9.26	F_A −46.2	
							F_B −34.8	−36.3
							J_{FF} = 563	
7	25.22	3.17	21.99	25.04	3.19	22.81	−28.2	−40.2
8[e]	46.66	6.15	15.53	46.92	6.47	15.56	F_A −26.3	
							F_B −18.5	−22.3
							J_{FF} = 582	
9	29.56	2.98	20.69	29.94	3.30	20.25	−35.4	−60.2
10	33.18	3.71	19.35	33.65	3.80	19.15	−1840 Hz[f]	
							−1204 Hz	−38.4
							−1156 Hz	
							−536 Hz	
11							−29.1	−37.1
12	44.95	3.77	15.72	44.75	3.87	16.04	−31.7	−42.5
13[g]	37.58	2.45	14.61	37.36	2.66	15.03	−31.0	−48.3
14	42.41	3.56	14.84	41.82	3.09	15.33	−32.2	−49.5
15	32.55	2.13	12.65	32.68	2.33	12.59	−30.9	−48.8

[a] At 40 MHz in CCl_4 or $CDCl_3$ solution. Usually, CCl_3F was the internal standard. ϕ values are parts per million from CCl_3F. J values are given in hertz. [b] F, 37.1 (calcd 37.0); bp 55° (50 mm); $n^{20}D$ 1.3940. [c] Mp 41–43°; F, 26.3 (calcd 26.4). [d] Cl, 26.2 (calcd 26.3). [e] F, 31.9 (calcd 31.6). [f] Appears to be AA′BB′ spectrum. [g] Cl, 12.0 (calcd 12.3); F, 33.3 (calcd. 33.0).

TABLE III

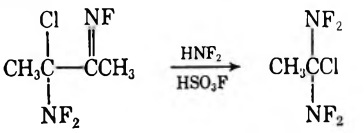
α-DIFLUORAMINO FLUORIDES

Fluorimine	Product	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
16	19	42.99	2.58	7.16	43.28	2.87	7.89
17	20[a]	35.03	2.10	5.84	35.69	2.55	6.40
2	21	54.86	4.60	8.00	54.78	4.80	8.40
18	22	35.92	4.02	13.97	35.72	4.30	14.17
8	23	46.66	6.15	15.55	46.73	6.40	15.80
9	24	29.56	2.98	20.69	30.28	3.20	22.09

[a] *Anal.* Calcd: F, 23.75; Br, 33.3. Found: F, 23.9; Br, 33.1.

expected as a consequence of the added stability of the α-phenylcarbonium ion.[15]

When we turned our attention to the α-halofluorimines **4** and **5**, it became evident that fluorosulfonic acid was a reagent of choice for fluorimine cleavages.



4 **26**

TABLE IV

1,1-BIS(DIFLUORAMINO)-1-HALOALKANES FROM FLUORIMINES AND HNF_2

Fluorimine	Product	Acid used	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % F	Found, % C	Found, % H	Found, % N	Found, % F	^{19}F nmr spectra,[a] ϕ[b]
4	26	HSO_3F	54	14.42	1.81	16.83	45.6	14.12	2.01	16.69	45.4	−34.7
16	27	BF_3 or H_2SO_4	60	36.78	2.20	12.26	33.3	37.38	3.10	13.07	35.8	−37.1
17	28	H_2SO_4	41	30.79	1.85	10.26	29.3	31.41	2.18	10.76	28.1	−44.0
25	29	HSO_3F	59	39.63	2.38	13.21		39.69	2.88	14.22		−23.6[c]
18	30	HSO_3F	23	30.85	3.45	17.99	32.5	31.23	3.80	18.53	32.8	F_A −35.2, F_B −33.9, J_{FF} = 605
8	31	HSO_3F	15	39.44	5.20	19.71		39.53	5.35	20.14		−27.5
6	32	H_2SO_4	72	27.34	1.31	9.11	24.7	28.07	1.61	9.77	25.11	−37.5

[a] At 40 MHz with CCl_3F internal standard. *J* values are given in hertz. [b] ϕ value are parts per million from CCl_3F. [c] C-F resonance at ϕ +152.4.

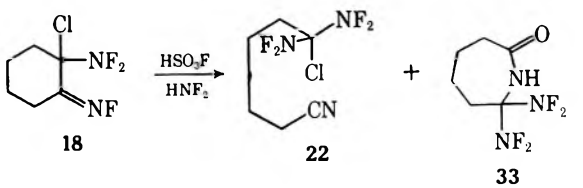
difluoramine under acidic conditions.[9,10] Conversion of α-halofluorimines into tris(difluoramino)alkanes was never accomplished.[10]

As part of this study, some of the α-difluoraminofluorimines were exposed to boron trifluoride (without added difluoramine). This Lewis acid, that neither complexes nor destroys HNF_2 at ordinary temperature,[11] appeared to be a particularly promising reagent for Beckmann cleavages of fluorimines. In these experiments without added difluoramine, fluoride ion appeared to be an effective trap for the α-difluoramino carbonium ion.[12,13] Table III summarizes characterization of the α-difluoramino fluorides produced in this way. When difluoramine was present, fluoride ion did not compete effectively with HNF_2 for the carbonium ion.[14]

The preliminary experiments that suggested the synthetic possibilities of fluorimine cleavages in the presence of difluoramine were conducted with fluorimines **1**, **2**, and **3**. Both **1** and **3**, upon treatment with HNF_2 and neat 96 or 100% sulfuric acid, gave 2,2-bis(difluoramino)propane. Fluorimine **2**, however, gave acetophenone (after hydrolysis), indicating that cleavage indeed occurred, but that the intermediate carbonium ion did not readily alkylate HNF_2. In view of the similar results obtained when acetophenone was exposed to HNF_2/H_2SO_4 under similar conditions,[2] this was

Fluorimine **4** gave 1-chloro-1,1-bis(difluoramino)ethane (**26**) cleanly. However, only trace amounts of 1-bromo-1,1-bis(difluoramine)ethane could be obtained from α-bromofluorimine **5** and HNF_2 with either fluorosulfonic or sulfuric acid. Bromine was liberated in these experiments. The results of these experiments, as well as related work, are summarized in Table IV.

With the cyclohexylfluorimine **18**, the main product was the chlorobis(difluoramino)nitrile **22** (23%), although a small amount of amide **33** also was isolated.



18 **22** **33**

Intramolecular cyclization of the capronitrile **22** could give rise to **33**, but there was no evidence for the formation of the amide when a sample of **22** was subjected to HSO_3F and HNF_2. In view of the results of rearrangements conducted in the presence of BF_3 (see below) it is more likely that a route such as is sketched leads to **33** (Scheme II).

Amide **33**, mp 70–71°, was characterized by a ^{19}F nmr peak at ϕ −24.7, and ^1H nmr peaks at τ 2.3 (NH) and at 115–155 Hz in a ratio of 1:8; no ^1H signal at τ 6.8, characteristic of the CH_2NH– function of caprolactam, was evident.

The three α-aryl-α-halo-α-difluoraminofluorimines **6**, **16**, and **17** were converted into α,α-bis(difluoramino)-α-halotoluenes. Here, the favorable experimental environment include sulfuric acid as catalyst and methy-

(9) 2-Chloro-2-difluoraminopropane, however, was successfully converted into 2,2-bis(difluoramino)propane: Dr. K. Johnson, Rohm and Haas Co., unpublished.

(10) Certain α-phosphato-α-difluoraminofluorimines could be converted into tris(difluoramines) in one step as discussed below.

(11) A. D. Craig, *Inorg. Chem.*, **3**, 1628 (1964).

(12) For a preliminary report, see T. E. Stevens, *Tetrahedron Lett.*, 3017 (1967).

(13) For examples of chloride ion functioning in a similar way in Beckmann fragmentation, see A. Hassner and E. G. Nash, *ibid.*, 525 (1965), and M. Ohno and I. Terasawa, *J. Amer. Chem. Soc.*, **88**, 5683 (1966).

(14) The last entry in Table III, **24**, was isolated from a reaction conducted with HNF_2 present.

(15) Under more stringent conditions, acetophenone can be converted into 1,1-bis(difluoramino)-1-phenylethane, and a small amount of the bis(difluoramino)ethane could be obtained from **2**, BF_3, and HNF_2.

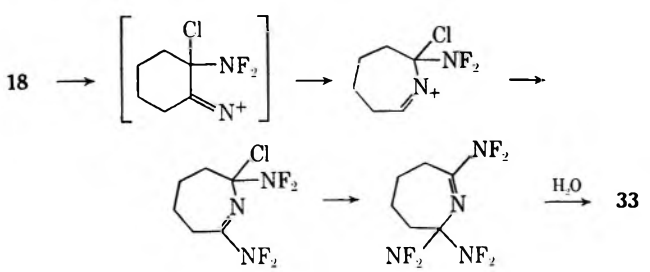
TABLE V

1,1,1-TRIS(DIFLUORAMINO)ALKANES

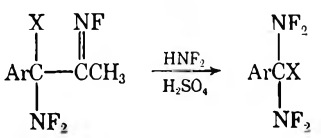
Fluorimine	Tris(difluoramine)	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	^{19}F nmr spectra, ϕ[a]
34 or 7	$CH_3C(NF_2)_3$	3							−28.0
12 or 35	36[b]	17	34.29	2.06	17.15	34.67	2.37	17.73	−27.8
14	p-$CH_3OC_6H_4C(NF_2)_3$ (37a)	12	34.92	2.56	15.27	34.51	2.89	14.58	−26.9
13	p-$ClC_6H_4C(NF_2)_3$ (37b)	c	30.07	1.44	15.03	30.05	1.69	15.11	−28.0
9	$NC(CH_2)_3C(NF_2)_3$ (38)	15	25.43	2.56	23.73	26.56	2.68	24.01	−27.7
10	$NC(CH_2)_4C(NF_2)_3$ (39)	11	28.81	3.22	22.40	28.42	3.44	21.87	−27.7
11	$CN(CH_2)_3C(NF_2)_3$	8	31.82	3.82	21.21	31.89	4.05	20.74	−27.5

[a] At 40 MHz in CCl_4 solution. ϕ values are in parts per million from internal CCl_3F. [b] F, 45.8 (calcd 46.5). [c] This material had a high vapor pressure, about 60 mm at 30°, and its isolation by chromatographic and distillation techniques was very inefficient.

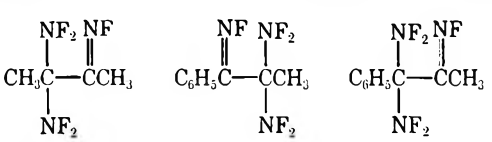
SCHEME II



iene chloride as solvent. Without solvent, the interaction of the fluorimine and sulfuric acid was difficult to control and often gave an exothermic decomposition that resulted in formation of the benzoic acid corresponding to the aryl group. Conversion of **16** into **27** with boron trifluoride was equally effective.



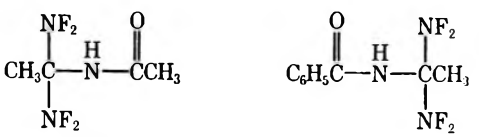
Reaction of α,α-Bis(difluoramino)fluorimines.—Attention then was shifted to α,α-bis(difluoramino)-fluorimines. On the basis of the experiences with α-halofluorimines, the three fluorimines **7**, **34**, and **35** were chosen for further study. The close electronic relationship of **4** and **7** is obvious, while with **34** formation of benzonitrile might be expected to aid the initial carbon–carbon bond cleavage. In **35** the aromatic ring



should stabilize the bis(difluoramino)-substituted carbonium ion. The preparation of **34** and **35** was reported recently.[3]

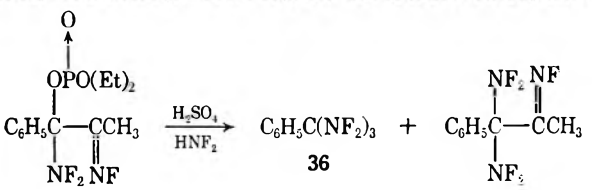
Only very small amounts of 1,1,1-tris(difluoramino)-ethane (from **7** or **34**) and α,α,α-tris(difluoramino)-toluene (from **35**) could be obtained by cleavage and difluoramination using sulfuric or fluorosulfonic acids. The tris(difluoramino)ethane was characterized only by spectral data. Table V summarizes the characterization of the tristoluene and other 1,1,1-tris(difluoramino) compounds.[16,17]

Amides **45** and **46** were obtained in low yield (up to 30%) from **7** and **34**, respectively. In sulfuric acid, fluorimine **35** was converted into benozic acid rather than a difluoraminoamide.[18] Apparently the com-



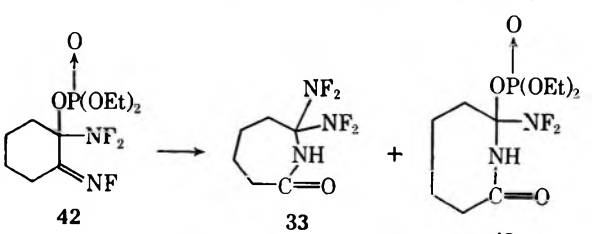
45 **46**

(16) The possibility that α-phosphato-α-difluoraminofluorimines such as **41**, often used as precursors to α,α-bis(difluoramino)fluorimines,[3] could be converted directly into the tris(difluoramino)alkanes was explored in some detail. This would, of course, shorten the sequence considerably. Phosphate **41**, which would give about 50% **35**,[3] was converted directly into **36**



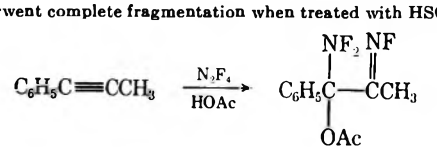
41 **36** **35**

(3% yield) with a longer reaction time. Under the same reaction conditions (30% fuming sulfuric acid), **35** gave **36** (5% yield). With fluorosulfonic acid, Beckmann and related rearrangements (discussed below) of **41** began to predominate. So, only with **41**, and the related 4-chlorophenyl example outlined in the Experimental Section, was the procedure successful. Fluorimino phosphate **42** could be converted into amides **33** and **43**; the same results were obtained with the fluorimino phosphate of the cyclopentyl series.



42 **33** **43**

The fluorimino acetate **44**, prepared from phenylmethylacetylene and N_2F_4,[17] underwent complete fragmentation when treated with HSO_3F/HNF_2.



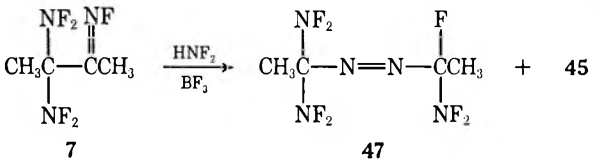
44

(17) W. H. Graham, 154th National Meeting of the American Chemical Society, Chicago, Ill., 1967, Abstract S-159.

(18) The α,α,α-tris(difluoramino)toluenes, in particular, were rather sensitive to strong acid, and readily liberated difluoramine. Thus, the same conditions that gave fragmentation of the fluorimine destroyed the desired product. This instability of the tris(difluoramino) was a limitation that was never successfully circumvented; the amount of trisalkane formed and destroyed was never determined.

bined electronegativity of the two difluoramino groups hinders the cleavage necessary to produce 1,1-bis(difluoramino)carbonium ions. Instead, an ordinary Beckmann rearrangement with migration of the bis(difluoramino)alkyl fragment predominates.

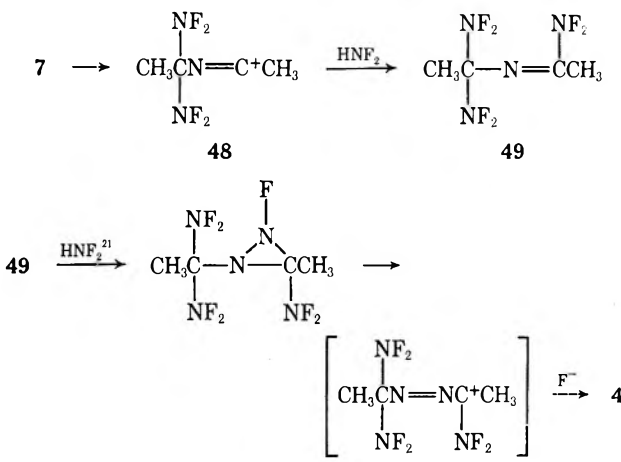
Rather unexpected rearrangements were encountered when boron trifluoride was used with fluorimines **7** and **35**. No detectable 1,1,1-tris(difluoramino)ethane was isolated from **7**, HNF_2, and BF_3. The major volatile product (about 15% yield) was assigned structure **47** on the basis of the elemental analysis and spectral data



7 **47**

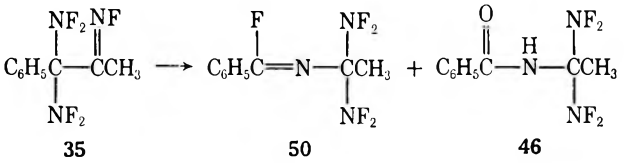
given in the Experimental Section. Amide **45**, 34%, was obtained after hydrolysis of the reaction residue.

Of all the fluorimines examined here, only **7** gave isolable quantities of an azo compound such as **47**. Formation of **47** can be explained, however, in terms of processes familiar to difluoramine chemistry.[19] Presumably, one of the initial products of the interaction of **7** and BF_3 would be a carbonium ion such as **48**.[20] Formation of imine **49**, or a related species,[21] would give an imine that might give an N-fluorodiaziridine. Re-



arrangement of this diaziridine in the manner shown, a process analogous to some proposed for reactions of imines and HNF_2,[19] would lead to **47**. Internal return of fluoride ion predominates in such processes.[17,19]

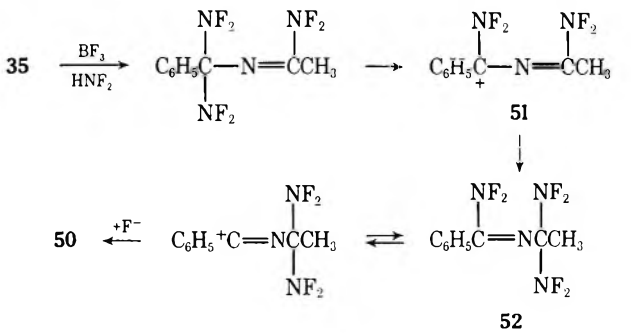
The products obtained from **35**, BF_3, and HNF_2 were the C-fluorimine **50** (56%) and amide **46** (about 15%). The structure of imine **50** was evident from its spectral properties. The infrared spectrum had strong C=N absorption at 5.80 μ; ^{19}F nmr peaks at ϕ −27.5 (4 F)



35 **50** **46**

and ϕ +25.4 (1 F) were observed. In the ^{1}H nmr spectrum, the methyl group next to the geminal difluoramino function was evident; a single peak at τ 8.02 with J_{HF} = 2 Hz was present. The aromatic ring protons were at τ 1.92 (2 H) and 2.44 (3 H). Hydrolysis of **50** produced **46**.

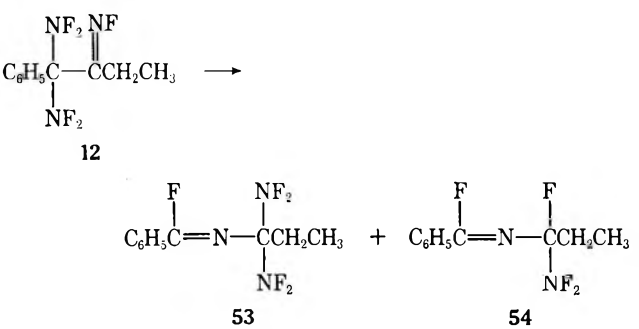
This surprising reorganization of **35** is probably due to an initial Beckmann rearrangement, followed by alkylation of difluoramine by the resulting carbonium ion. Possibly, the added stability of cation **51** contributes to the rearrangement to **52**. Imine **52** may well be the material that hydrolyzes to produce amide **46**. The C-fluorimine **50** may arise when fluoride ion irreversibly traps the carbonium ion formed when **52** ionizes as shown.



51

52

No α,α,α-tris(difluoramino)toluene appeared to form from either **35**, BF_3, and HNF_2, or from the closely related fluorimine **12** and the same reagents. Another imine, **54**, as well as expected products **53** and the benzamide derived from **53**, was obtained from **12**. Probably, **54** arises from fluoride ion trapping either the initial carbonium ion or one of the other intermediates that usually leads to **50** or **53**.



12

53 **54**

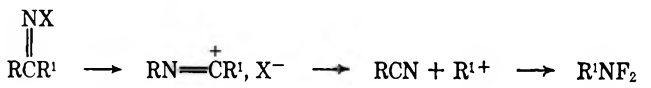
Both the 4-chloro- and 4-methyoxyphenylfluorimines (**13** and **14**, respectively) gave small amounts of the corresponding tris(difluoramino)toluene under the BF_3–HNF_2 reaction conditions. The major products, however, were the C-fluorimines related to **50**. Details of these reactions are given in the Experimental Section. Apparently both the 4-chloro- and the 4-methoxy substituents contribute sufficiently to the stability of the α,α-bis(difluoramino)carbonium ion to allow cleavage to compete with the rearrangement.

(19) W. H. Graham, *J. Amer. Chem. Soc.*, **88**, 4677 (1966).

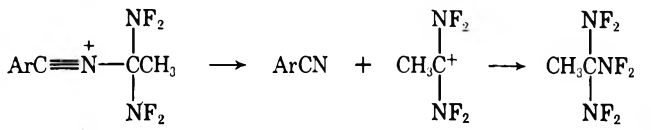
(20) Very likely it is a nitrilium tetrafluoroborate, $CH_3C(NF_2)_2{}^+N{\equiv}CCH_3$, $BF_4{}^-$; see C. A. Grob, H. P. Fischer, W. Rondenbusch, and J. Zergeny, *Helv. Chim. Acta*, **47**, 1003 (1964). Attempts to obtain definitive nmr and infrared spectra of nonvolatile residues from these BF_3 reactions were not successful; solubility was a major problem. Since any C-fluoro- or C-difluoraminoimine such as **49**, possible precursors to amide **45**, would be volatile enough to be removed from the reaction mixture *in vacuo*, some nonvolatile, insoluble salt must remain and give **45** upon hydrolysis.

(21) Variations of this route are equally possible. Fluoride ion, instead of difluoramine, could add to the initial carbonium ion **48**, and difluoramine could be trapped by the α-azocarbonium ion. Addition of HNF_2 to the imine may be a stepwise process, rather than the insertion of NF nitrene pictured.[19]

Since there is evidence that carbonium–nitrilium ions from the Beckmann rearrangement may be formed and then fragment,[20] the possibility that fluorimines **35**, **12**, **13**, and **14** might yield not α,α,α-tris(difluoramino)-toluene, but rather 1,1,1-tris(difluoramino)ethane, was

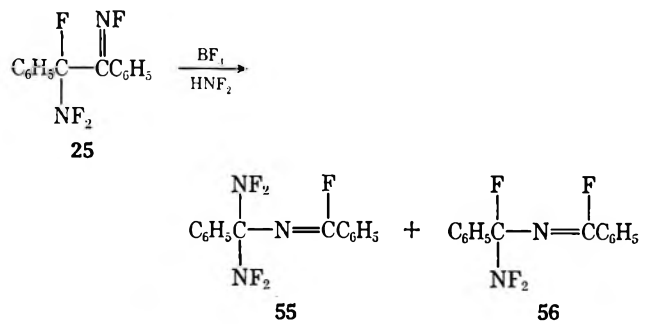


not overlooked. That is, there was no evidence that the α-aryl carbonium ions postulated in the scheme above fragmented as shown. The reaction products



were carefully monitored for the presence of the tris-(difluoramino)ethane; it was never detected.

Although the α,α-bis(difluoramino)-α-fluorotoluene (**29**) reported in Table IV was formed from **25**, HNF_2, and HSO_3F, treatment of **25** with BF_3, with or without

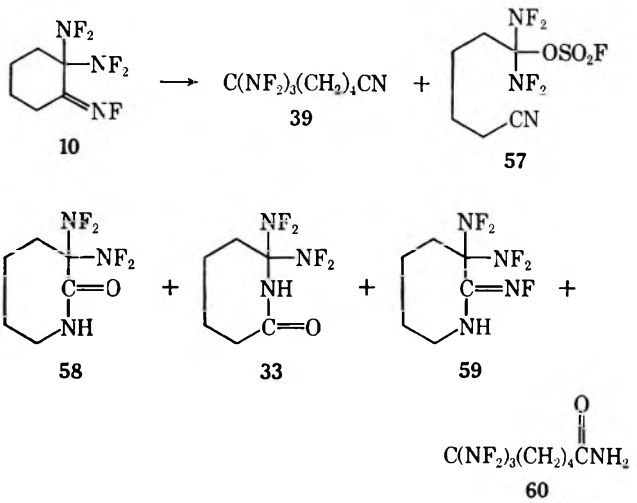


HNF_2 present, gave a mixture of **55** and **56**.[22] Imines **55** and **56** were never completely separated from one another, but variations in the composition of the mixtures allowed the ^{19}F nmr peaks at ϕ −28.1 [multiplet, —$C(NF_2)_2$] and ϕ +15.7 (multiplet, CF) to be assigned to **55**, and the peaks at ϕ −20.7 (NF_2), +29.5 (doublet, J_{FF} = 18 Hz, FC=N), and +124.3 (doublet, J_{FF} = 18 Hz, CF) to be assigned to **56**.

It should be noted, however, that cleavage was the predominant reaction when the α-halofluorimines **16** and **17** were exposed to BF_3. Perhaps a trace of imine **50** was formed from **17**, BF_3, and HNF_2, but the reaction was not of preparative significance.

Also, there was no indication that the C-fluorimines such as **50** would react further with difluoramine to give N-fluorodiaziridines or azo materials such as **47**. The imines were recovered unchanged after treatment with HNF_2–BF_3 or HNF_2–sodium fluoride.

For further study of α,α-bis(difluoramino)fluorimines, the cyclic fluorimines **9**, **10**, and **11** were selected. Of these three, **10** was examined most carefully. Initial experiments conducted with **10**, sulfuric acid, and difluoramine gave no tris(difluoramine); with **10**, BF_3, and HNF_2, C-fluoro products complicated the reaction mixture. Fluorosulfonic acid seemed to lead to appreciable amounts of the product sought—6,6,6-tris(difluoramino)hexanenitrile (**39**)—so the materials formed from the reaction of **10**, HNF_2 and HSO_3F in methylene chloride or 1,1,2-trichlorotrifluoroethane solution were characterized. These products included compounds **33**, **39**, **57**, **58**, **59**, and **60**.[23]



Nitrile **39** formed to the extent of 5–12% of theory, while less than 5% of its hydrolysis product, amide **60**, was usually present. Amide **33**, the "expected" Beckmann rearrangement product, and its structural isomer, amide **58**, were usually the major products here (25–40% of theory). Amide **33** usually predominated in the fluorosulfonic acid runs, but in sulfuric acid **58** was the major product. Fluorosulfate **57** was apparently an initial product of the cleavage reaction, and was converted into nitrile **39** under the reaction conditions. Appreciable quantities (5–10%) of **57** were encountered only with limited reaction times.[24] The yield of fluorimine **59**, which appeared to be stable under the reaction conditions, was 5–15%.

Amide **58**, mp 109–110°, had a single ^{19}F nmr peak at ϕ −26.5. The ^1H nmr clearly showed the $-CH_2N-$ peak at τ 6.6. Fluorosulfate **57** had ^{19}F nmr peaks at ϕ −48.3 (SF) and −25.6 (NF). Fluorimine **59** had peaks at ϕ −27.4 and −26.7 due to the geminal difluoramine, and at ϕ +41.2, doublet J_{HF} = 8 Hz, due to C=NF. The addition of trifluoroacetic acid, or heterodecoupling, collapsed the ϕ +41.2 peak to a singlet.

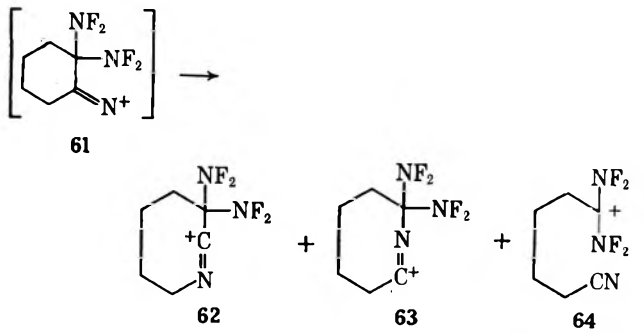
The isolation of appreciable amounts of amide **58** shows a nonstereospecific Beckmann rearrangement occurs. Whether this is due to isomerization of the fluorimine under the reaction conditions, so that *trans* migration of the methylene group led to **58** or whether an intermediate close to immonium cation **61**[25] rearranges and fragments as shown is not known.

(22) The reaction was much cleaner with HNF_2 present; appreciable tarring occurred in its absence.

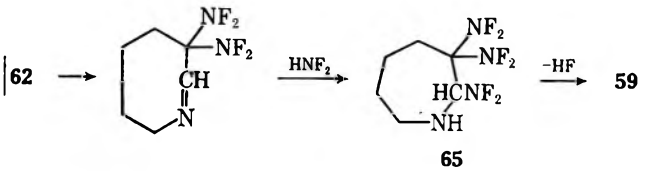
(23) The presence of 1,1-bis(difluoramino)-2-aza-3-fluoro-2-cycloheptene was often indicated by ^{19}F nmr peaks at ϕ −26.6 and +29.2, but this material was never completely characterized. On hydrolysis, however, it gave amide **33**.

(24) This fluorosulfate (**57**) could be converted into **39** by further exposure to HNF_2 and fluorosulfonic acid.

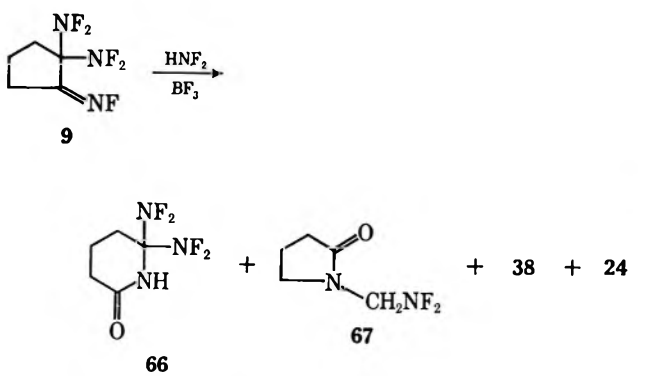
(25) P. T. Lansburg and N. R. Mancuso, *J. Amer. Chem. Soc.*, **88**, 1205 (1966); *Tetrahedron Lett.*, 2245 (1965).



Certainly, cation **62** is the logical precursor of both amide **58** and imine **59**. Reduction of some intermediate is necessary to produce **59**; the material reduced may well be ion **62**.[26] Difluoramine, present in excess, may participate in this reduction, although examples of related reductions (without HNF_2) have been reported.[26] Addition of difluoramine to imine shown gives **65**; loss of HF then produces **59**.

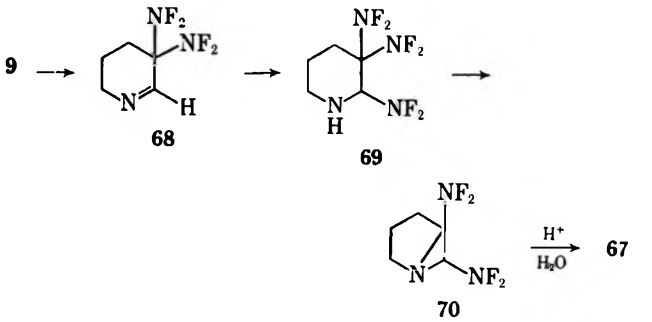


The preparation of the cyclopentylfluorimine **9** was hindered by difficulties reported elsewhere.[3] Limited experiments with **9**, however, indicated that cleavage and difluoramination to give 5,5,5-tris(difluoramino)-pentanenitrile (**38**, Table V) proceeded with the same limited success encountered in the cyclohexyl series. In addition to **38**, 5,5-bis(difluoramino)-5-fluoropentanenitrile (**24**, Table II), a small amount of amide **66**, and another rearrangement product, pyrrolidone **67**, were obtained from **9**, HNF_2, and BF_3.



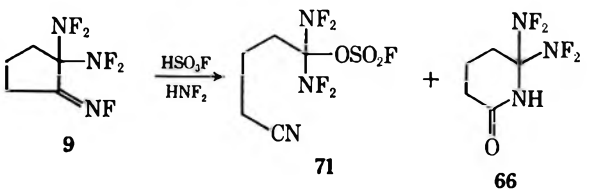
The identity of N-(difluoraminomethyl)pyrrolidone (**67**) was established by an independent synthesis from pyrrolidone and difluoraminomethanol[27] and by the spectral properties that follow. The infrared spectrum of **67** had strong 5.8-μ carbonyl absorption; the ^{19}F nmr spectrum had a peak at ϕ −43.4, triplet, J_{HF} = 24 Hz. In the ^1H nmr spectrum of **67**, the $-CH_2NF$ peak was a triplet, J_{HF} = 24 Hz at τ 5.16, the $-CH_2N-$ peak at τ 6.35 was also a triplet, J_{HH} = 7 cps, and the remaining four ring protons were a multiplet centered at τ 7.64.

The mechanism of formation of **67** is obscure, but the following rationale is proposed. Reduction of the carbonium ion produced by migration of the methylene group would produce imine **68**. A similar reduction

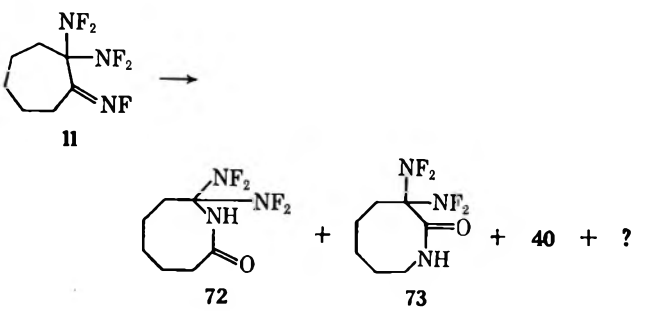


was postulated in the cyclohexyl series just discussed. Here, however, addition of difluoramine to the imine gives an adduct (**69**) that reacts further in a manner different than **65**. Intramolecular loss of HNF_2 from **69** would give bicyclic difluoramine **70**,[28] a possible precursor to **67**.

With fluorosulfonic acid and a limited reaction time, fluorosulfate **71** (17%) and amide **66** (7%) were the major products from **9**. With difluoramine and sulfuric acid, **71** was converted into the tris(difluoramino)-pentane **38**.



The cycloheptylfluorimine **11** gave products expected on the basis of experience with the five- and six-ring systems. Amides **72** (3%), mp 85–87°, and **73** (12%), mp 71–73°, along with 7,7,7-tris(difluoramino)heptanenitrile (**40**, Table IV) and a material of unknown structure were obtained with fluorosulfonic acid and difluoramine. Details are in the Experimental Section.



The geminal and trisdifluoramino compounds reported in this work are considerably more shock sensitive than nitroglycerin; they should be handled with great care.

Experimental Section

Melting points and boiling points are uncorrected. The ^{19}F nmr spectra were run in CCl_4 or $CDCl_3$ at 40 MHz on a Varian 4300B spectrometer; proton nmr spectra were recorded on a Varian A-60 spectrometer.

(26) For examples of reduction during Beckmann rearrangements, see R. T. Conley and M. C. Annis, *J. Org. Chem.*, **27**, 1961 (1962).

(27) A procedure developed by Imperial Chemical Industry: Dr. A. Dinwoodie, personal communication.

(28) For similar reactions of 3-chloropiperidine, 2-(chloromethyl)pyrrolidines, and bicyclic aziridines, see C. F. Hammer and S. R. Heller, *Chem. Commun.*, 919 (1966). For the parent bicyclic aziridine, see P. G. Gassman and A. Fentiman, *J. Org. Chem.*, **32**, 2388 (1967).

The reaction mixtures and products reported below must be considered explosive hazards. Adequate shielding must be employed at all times.

Preparation of 2-Methyl-2-difluoramino-3-(fluorimino)butane (1).—The addition of tetrafluorohydrazine to 2-methyl-2-butene, 7.0 g (0.10 mol), was carried out in 30 ml of methylene chloride at ambient temperature and 85 psi over a period of 90 hr.[1] The methylene chloride solution of the adduct was mixed with 100 ml of absolute ethanol and cooled in an ice bath while 70 ml of 1.43 *N* potassium hydroxide in 90% ethanol was added dropwise. A reaction temperature of 12–15° was maintained during this addition; the reaction mixture was then stirred for 1 hr at 25°. The mixture was diluted with salt water and extracted with methylene chloride. The extract was washed three times with water and dried over magnesium sulfate. Distillation of the extract through a Holtzmann column gave, after removal of the methylene chloride, 2-methyl-2-difluoramino-3-fluoriminobutane (1): 7.85 g, bp 55° (50 mm), n^{20}D 1.3940.

Preparation of 1-Phenyl-1-fluorimino-2-methyl-2-(difluoramino)propane (3).—A solution of 9.1 g (38.6 mmol) of the tetrafluorohydrazine–β,β-dimethylstyrene adduct in 70 ml of ethanol was cooled in an ice bath while 30 ml of 1.30 *N* potassium hydroxide in 90% ethanol was added dropwise. After the mixture had stirred for 1 hr at 25°, it was processed as described above. Distillation gave 6.1 g of product, bp 50° (1 mm). After chromatography on silica gel (elution with pentane–methylene chloride, 3:1) and recrystallization from hexane, the 1-phenyl-1-fluorimino-2-methyl-2-(difluoramino)propane (3) was obtained as white crystals, mp 41–43°.

Preparation of 2-Chloro-2-difluoramino-3-(fluorimino)butane (4).—The product from the reaction of 2-chloro-2-butene (10.0 g) and tetrafluorohydrazine in methylene chloride solution was diluted to 60 ml with methylene chloride. A 10-ml sample of this solution was distilled in the Holtzmann column; 2-chloro-2,3-bis(difluoramino)butane [2.2 g, bp 50° (40 mm)] was obtained.

Anal. Calcd for $C_4H_7ClN_2F_4$: C, 24.69; H, 3.63; N, 14.40. Found: C, 25.60; H, 4.08; N, 14.94.

The remainder of the methylene chloride solution was treated with 62 ml of 1.45 *N* potassium hydroxide in ethanol in the manner described above. The product, 2-chloro-2-difluoramino-3-(fluorimino)butane (4), 7.65 g, was isolated by distillation, bp 48° (52 mm).

Preparation of 2-Bromo-2-difluoramino-3-(fluorimino)butane (5).—The addition of tetrafluorohydrazine to 2-bromo-2-butene (10.0 g) was carried out as usual (80°, 80 psi) in 30 ml of methylene chloride. The solution from the reactor was diluted with 100 ml of ethanol and the mixture was stirred with ice-bath cooling while 54 ml of 1.38 *N* potassium hydroxide in 90% ethanol was added dropwise. When the addition of base was completed the solution was stirred at 25° for 1 hr. Water was added and the organic product was extracted with methylene chloride. The extract was distilled through a Holtzmann column and gave the fluoriminobutane (5), 11.5 g, bp 60° (62 mm).

Dehydrofluorination of 2,2,3-Tris(difluoramino)butane.—A solution of 1.74 g of 2,2,3-tris(difluoramino)butane[2] in 10 ml of methylene chloride and 10 ml of methanol was stirred in an ice bath while 19.5 ml of 0.43 *N* sodium methoxide in methanol was added dropwise. When addition of methoxide was complete, the cooling bath was removed and the solution allowed to warm to 15°. The reaction mixture was poured into water and extracted with methylene chloride. The organic extract was dried over magnesium sulfate and concentrated to about 3 ml by distillation. The residue was fractionated *in vacuo* through 0, −45, and −80 baths. The −45° fraction, 1.0 g, was 2,2-bis(difluoramino)-3-(fluorimino)butane (7). A small amount of methylene chloride and, in some cases, a less volatile material (mostly retained in the 0° trap) contaminated the sample. A sample for analysis was purified by vpc at 75° on a silicone (GE SF-96) column.

Preparation of 1,1-Bis(difluoramino)-2-(fluorimino)cyclohexane (10).—A solution of 2.15 g of 1,1,2-tris(difluoramino)cyclohexane[2] in 20 ml of methylene chloride and 25 ml of methanol was stirred in an ice bath while 6.5 ml of 1.42 *N* sodium methoxide in methanol was added dropwise. The solution was stirred 15 min, then poured into ice water. The organic product was taken up in methylene chloride. The residue obtained upon evaporation of the methylene chloride was transferred with gentle warming into a −25° trap *in vacuo* to give 1,1-bis(difluoramino)-2-(fluorimino)cyclohexane (10), a colorless liquid.

1,1-Bis(difluoramino)-1-*p*-methoxyphenyl-2-(fluorimino)propane (14).—1-(Diethylphosphato)-1-difluoramino-1-*p*-methoxyphenyl-2-(fluorimino)propane was prepared from *p*-methoxypropiophenone in the usual way[3] and was characterized by ^{19}F nmr spectrum. Peaks at −1782, −1208, −1104, and −532 Hz (40 MHz, CClF standard) were observed for the $-NF_2$ quartet, while the C=NF peak was at ϕ −33.6. From 20 g of the phosphate in methylene chloride and difluoramine–sulfuric acid (1 hr, 15°) was obtained 1,1-bis(difluoramino)-1-(*p*-methoxyphenyl)-2-fluoriminopropane (14, 2.6 g) as an oil.

Reactions of 1,1-Bis(difluoramino)-1-*p*-methoxyphenyl-2-(fluorimino)propane, Difluoramine, and Boron Trifluoride.—A mixture of 0.85 g (3 mmol) of the fluorimine 14, 90 ml (STP) of boron trifluoride, 110 ml (STP) of difluoramine, and 2 ml of methylene chloride in a pressure tube[29] was stirred at 0° for 90 min. The tube was vented and the residue was removed with a methylene chloride–water mixture. The organic product, isolated in methylene chloride, was chromatographed on a silica gel column. Elution of the column with pentane–methylene chloride (4:1) gave α,α,α-tris(difluoramino)-*p*-methoxytoluene (37a), 0.102 g, as an oil, ^{19}F nmr single peak at ϕ −26.9.

The next fraction from the column (3:1 pentane–methylene chloride) was 1-fluoro-1-(*p*-methoxyphenyl)-2-aza-3,3-bis(difluoramino)-1-butene, 0.095 g.

Anal. Calcd for $C_{10}H_{10}N_3F_5O$: C, 42.41; H, 3.56; N, 14.84. Found: C, 42.16; H, 3.65; N, 13.97.

The ^{19}F nmr spectrum showed a peak at ϕ −26.9 (geminal NF_2's) and at +27.7 [-(F)C=N].

1,1-Bis(difluoramino)-1-phenyl-2-(fluorimino)butane (12).—The usual procedure was followed to prepare 1-phenyl-1-difluoramino-1-(diethylphosphato)-2-(fluorimino)butane;[3] this phosphate was characterized by ^{19}F nmr. The NF_2 quartet (40 MHz, CCl_3F standard) was at −1776, −1196, −1080 and −504 Hz and the C=NF absorption was at ϕ −28.6.

From 19.2 g of this phosphate, after exposure to difluoramine-sulfuric acid, was obtained 1,1-bis(difluoramino)-1-phenyl-2-fluoriminobutane (12), 6.2 g. The fluorimine was purified by silica gel chromatography.

Reaction of 1,1-Bis(difluoramino)-1-phenyl-2-(fluorimino)-butane, Difluoramine, and Boron Trifluoride.—A mixture of 0.80 g (3 mmol) of the fluorimine 12, 4 mmol of boron trifluoride, 5 mmol of difluoramine, and 3 ml of methylene chloride was stirred overnight at ambient temperature in a Fischer–Porter pressure tube.[29] The tube was vented and the residue was partitioned between water and methylene chloride. The organic residue was chromatographed on silicic acid, but pentane eluted 0.35 g of mixed materials. This fraction was rechromatographed on silica gel. The first fraction eluted was 1-fluoro-1-phenyl-2-aza-3,3-bis(difluoramino)-1-pentene (53), an oil.

Anal. Calcd for $C_{10}H_{10}N_3F_5$: C, 44.95; H, 3.77; N, 15.72; F, 35.6. Found: C, 44.57; H, 3.99; N, 16.15; F, 37.0.

The ^{19}F nmr spectrum showed peaks at ϕ −27.0 and −26.6 (geminal NF_2's) and at +23.8 (-CF=N).

The next fraction eluted was 1,3-difluoro-1-phenyl-2-aza-3-difluoramino-1-pentene (54), also an oil.

Anal. Calcd for $C_{10}H_{10}N_2F_4$: C, 51.28; H, 4.30; N, 11.96; F, 32.45. Found: C, 51.41; H, 4.70; N, 11.34; F, 31.9.

The ^{19}F nmr spectrum showed peaks at ϕ −19.0 ($-NF_2$), +33.6 (doublet J_{FF} = 24 Hz, due to -(F)C=N-, and a multiplet centered at +128.3.

Observing ^{19}F and irradiating ^{1}H, the upfield peak collapses to a doublet. Homodecoupling the upfield peaks was not successful, but they are almost certainly due to F–F coupling. No evidence of H–F coupling was noted observing the ϕ 33.6 peak while irradiating ^{1}H.

Crude samples of N-[1,1-bis(difluoramino)-1-propyl]benzamide were eluted later from the column. The sample characterized was prepared by hydrolysis of the C-fluorimine in aqueous methanolic hydrochloric acid (50°, 1 hr). It was recrystallized from hexane, mp 79–81°.

Anal. Calcd for $C_{10}H_{11}N_3F_4O$: C, 45.28; H, 4.18; N, 15.85; F, 28.7. Found: C, 45.61; H, 4.36; N, 15.42; F, 29.4.

The ^{19}F nmr spectrum showed a single peak at ϕ −24.6.

Reaction of 1-(4-Chlorophenyl)-1-difluoramino-1-(O,O-diethylphosphoryloxy)-2-(fluorimino)propane and Difluoramine.—A 15-g sample of the above fluoriminophosphate in 10 ml of methylene chloride was added to excess difluoramine refluxing over 20 ml of 30% fuming sulfuric acid. After a contact time of 130 min at

(29) Described by R. P. Rhodes, *J. Chem. Educ.*, **40**, 423 (1963).

15–25°, excess methylene chloride was added, the acid layer was separated, and the organic solution was washed with water and aqueous sodium bicarbonate. The residue obtained upon evaporation of the solvent was chromatographed on silica gel. The first fraction eluted from the column (pentane–methylene chloride, 19:1) was α,α,α-tris(difluoramino)-4-chlorotoluene (**37b**), 0.23 g.

The ^{19}F nmr spectrum showed a single peak at ϕ −28.0. The ^1H nmr spectrum showed only an aromatic multiplet centered at τ 2.55.

The next fraction eluted (by pentane–methylene chloride, 10:1) was 1,1-bis(difluoramino)-1-(4-chlorophenyl)-2-(fluorimino)propane (**13**), 2.1 g, a clear liquid.

Reaction of Boron Trifluoride and 1,1-Bis(difluoramino)-1-(4-chlorophenyl)-2-(fluorimino)propane.—A mixture of 1.44 g of the fluorimine **13**, 3 ml of methylene chloride, 80 ml (STP) of difluoramine, and 140 ml (STP) of boron trifluoride was stirred in a 15-ml Fischer–Porter pressure tube at 0° (30 min) and at ambient temperature (90 min). The tube was vented and the residue was partitioned between water and methylene chloride. The residue from the organic phase was chromatographed on silica gel. The first fraction from the column, 0.089 g, was α,α,α-tris(difluoramino)-4-chlorotoluene (**37b**). The next fraction eluted from the column was 2-aza-1-fluoro-1-*p*-chlorophenyl-3,3-bis(difluoramino)-1-butene, 0.93 g, a clear liquid.

Anal. Calcd for $C_9H_7ClN_3F_5$: C, 37.58; H, 2.45; N, 14.61; F, 33.0; Cl, 12.3. Found: C, 37.21; H, 2.68; N, 15.31; F, 34.4; Cl, 11.8.

The ^{19}F nmr spectrum showed peaks at ϕ −27.2 [$C(NF_2)_2$] and +27.7 [-(F)C=N-]. The ^1H nmr spectrum showed τ 2.28 (aromatic multiplet) and 8.01 ($-CH_3$). The next fraction from the column, 0.057 g, was recovered starting material. Methylene chloride eluted N-[1,1-bis(difluoramino)-ethyl]-*p*-chlorobenzamide, 0.10 g, mp 92–94° (from hexane).

Anal. Calcd for $C_9H_8N_3F_4ClO$: C, 37.84; H, 2.82; N, 14.71; F, 26.6. Found: C, 37.79; H, 2.92; N, 14.38; F, 26.1.

The ^{19}F nmr spectrum showed peaks at ϕ −23.9 and −24.4 (doublet). The ^1H nmr spectrum showed τ 2.37 (aromatic multiplet) and 7.73 ($-CH_3$).

Preparation of 6-Chloro-6-difluoramino-6-fluorohexanenitrile (22).—A mixture of 0.80 g (4 mmol) of 1-chloro-1-difluoramino-2-fluoriminocyclohexane, 5 ml of methylene chloride, and 90 cc (STP) of boron trifluoride was stirred in a pressure tube at 0° for 30 min and at ambient temperature for 2 hr. The tube was vented, and the residual methylene chloride solution was washed with aqueous sodium bicarbonate and water. This was combined with another run of the same size, and the product was chromatographed on silica gel. Elution of the column with pentane–methylene chloride (1:1) gave 6-difluoramino-6-fluoroheptanenitrile (**23**), 0.28 g.

The ^{19}F nmr spectrum showed peaks at ϕ −19.1 (NF_2) and +142.7 (CF).

Preparation of 6,6-Bis(difluoramino)heptanenitrile (31).—A mixture of 3 ml of methylene chloride, 3 ml of fluorosulfonic acid, and 8 mmol of difluoramine in a closed system was stirred at −20° while 0.90 g (5 mmol) of 1-difluoramino-1-methyl-2-(fluorimino)cyclohexane in 2 ml of methylene chloride was added dropwise. The reaction mixture then was stirred at 0° for 30 min and at ambient temperature for 2 hr. The difluoramine was pumped off and the residue poured over ice. The residue obtained after the usual extraction procedure was chromatographed on silica gel. The pentane–methylene chloride (1:1) eluates gave 6,6-bis(difluoramino)heptanenitrile (**31**), 0.16 g.

Preparation of α-Chloro-α-difluoramino-α-fluorotoluene (19).—A mixture of 0.71 g (3 mmol) of 1-chloro-1-difluoramino-1-phenyl-2-fluoriminopropane (**16**), 70 cc (STP) of boron trifluoride, and 5 ml of methylene chloride was sealed in a pressure tube at −80°. The mixture was warmed to −10° (10 min) and then 0° (1 hr) before the boron trifluoride was vented. The methylene chloride solution was washed (5% aqueous sodium bicarbonate and water) and dried. The organic phase was concentrated by distillation, then fractionated *in vacuo* through a −45° trap. The −45° trap retained α-difluoramino-α-fluorotoluene (**19**), 0.40 g.

Preparation of α,α-Bis(difluoramino)-α-fluorotoluene (29).—A mixture of 5 ml of methylene chloride, 2 ml of fluorosulfonic acid, and 7 mmol of difluoramine was stirred at −10° in a closed system while 1.13 g (4 mmol) of 1-difluoramino-1-fluoro-2-fluorimino-1,2-diphenylethane in 5 ml of methylene chloride was added dropwise. The mixture was then stirred at 0° for 1 hr. The HNF_2 was pumped off *in vacuo* and the residual mixture was poured on ice. The organic product was extracted into methylene chloride; the methylene chloride phase was washed with 5% aqueous sodium bicarbonate and water. When the extract had been concentrated to 1 ml by distillation, the residue was fractionated *in vacuo* through traps cooled to −45 and −80°. The −45° trap contained 0.67 g of benzonitrile (about 25% of total) and the desired product. Chromatography on a 0.25 in. × 5 ft Aerograph Dow 710 silicone on 60/80 Chromosorb B at 115° separated the benzonitrile (10-min retention) from α,α-bis(difluoramino) α-fluorotoluene (**29**) (4-min retention).

Reaction of Boron Trifluoride, Difluoramine, and 1-Phenyl-1-chloro-1-(difluoramino)-2-(fluorimino)propane.—A mixture of 0.72 g (3 mmol) of fluorimine **16**, 100 cc (STP) of difluoramine, 70 cc (STP) of boron trifluoride, and 2 ml of methylene chloride was stirred for 2 hr at ambient temperature in a Fischer–Porter pressure tube.[29] The tube was opened and the volatile contents were removed *in vacuo*. The residue in the tube was partitioned between water and methylene chloride. Concentration of the methylene chloride solution followed by distillation *in vacuo* through −25 and −80° traps gave, in the −25° trap, α-chloro-α,α-bis(difluoramino)toluene (**27**), 0.4 g, identified by infrared and nmr spectra. Only a trace of nonvolatile material remained in the distillation flask.

Preparation of α,α-Bis(difluoramino)-α-chlorotoluene (27).—A mixture of 4 ml of 100% sulfuric acid and 4 ml of methylene chloride was cooled to −115°, and 1.42 g (6 mmol) of 1-phenyl-1-chloro-1-difluoramino-2-(fluorimino)propane was added to the cold mixture. The mixture was degassed and then 150 ml (STP) of difluoramine was condensed into the U tube. The cooling bath was removed and the mixture was allowed to warm until it could be stirred magnetically; at this point an ice bath was placed around the U tube. After stirring for 35 min, the mixture was distilled *in vacuo* through −25, −80, and −115° traps. The −25° trap retained α,α-bis(difluoramino)-α-chlorotoluene (**27**), 0.86 g.

Preparation of 1-Chloro-1,1-bis(difluoramino)ethane (26).—Fluorosulfonic acid, 6 ml, was frozen, and 1.04 g (6 mmol) of 2-chloro-2-difluoramino-3-fluoriminobutane (**4**) was added to the solid acid. The mixture was degassed *in vacuo* and then 220 ml (STP) of difluoramine was condensed into the 300-ml reaction bulb. The cooling bath was removed, and the reaction mixture was allowed to come to ambient temperature. After the acid solution had been stirred for 90 min the mixture was pumped *in vacuo* through −80, −96, and −127° baths. 1-Chloro-1,1-bis(difluoramino)ethane (**26**), 0.54 g, was retained in the −80° trap.

Preparation of α,α-Bis(difluoramino)-α-bromotoluene (28).—A mixture of 4 ml of 100% H_2SO_4, 4 ml of methylene chloride, 1.68 g (6 mmol) of 1-phenyl-1-bromo-1-difluoramino-2-(fluorimino)-propane (**17**), and 230 ml (STP) of difluoramine was allowed to interact in the fashion described above. The reaction mixture was stirred 30 min at ice-bath temperature; then the excess difluoramine was removed *in vacuo*. The residual solution was poured over ice and the organic products were taken up in methylene chloride. The residue remaining (1.3 g) after evaporation of the methylene chloride was distilled *in vacuo* to give α,α-bis(difluoramino)-α-bromotoluene (**28**), 0.64 g. The residue from the distillation was starting material (nmr).

Reaction of 2-Chloro-2-difluoramino-1-(fluorimino)cyclohexane and Difluoramine.—Fluorosulfonic acid, 10 ml, was frozen and 2.12 g (10 mmol) of the fluorimine **18** was added to the frozen acid. The mixture was degassed, and difluoramine, 365 cc (STP), was condensed into the reaction flask. The mixture was allowed to warm to ambient temperature and was stirred for 45 min. After the volatiles had been pumped off *in vacuo*, the acid residue was poured over ice and the organic products were isolated by extraction with methylene chloride. The residue was chromatographed on a silica gel column packed in pentane–methylene chloride. Elution of the column with the same solvent gave 6-ehloro-6,6-bis(difluoramino)hexanenitrile (**30**), 0.52 g, as a liquid.

A solid was eluted from the column by methylene chloride–ethyl acetate (10:1); 0.09 g, mp 70–71° (from hexane), of 2-aza-3,3-bis(difluoramino)cycloheptanone (**33**) was obtained.

Anal. Calcd for $C_6H_9N_3F_4O$: C, 33.49; H, 4.22; N, 19.53; F, 35.3. Found: C, 33.42; H, 4.43; N, 18.80; F, 37.7.

Reaction of Boron Trifluoride, Difluoramine, and 2,2-Bis(difluoramino)-3-(fluorimino)butane.—A mixture of 0.60 g (3 mmol) of the fluorimine **7**, 40 cc (STP) of difluoramine, and 80 cc (STP) of boron trifluoride was stirred 20 hr at ambient tempera-

ture in a Fischer–Porter pressure tube. The reaction tube was cooled to −80°, opened, and pumped *in vacuo* through traps cooled to −45, −80, and −110°. The −45° trap retained 3,4-diaza-2,2,5-tris(difluoramino)-5-fluorohexane (**47**), 0.12 g, a pale yellow liquid. The analytical sample was purified by vpc on a GE silicon SF-96 column at 70°. The infrared spectrum exhibited no absorption in the 3.5–6.6-μ region; strong, broad peaks at 8.1, 8.4, 10, 10.7, 10.9, 112, and 12.6 μ were present.

Anal. Calcd for $C_4H_6N_5F_7$: C, 18.68; H, 2.35; N, 27.24. Found: C, 18.60; H, 2.33; N, 27.48.

The ^{19}F nmr spectrum showed peaks at ϕ −26.0, −19.5, and +132.2; ratio 4:2:1. The ^1H nmr showed $CH_3(NF_2)_2C$–, a quintet centered at τ 8.20, and $CH_3(NF_2)FC$–, at τ 8.15, doublet, J_{HF} = 18 Hz. Each member of the doublet was further split (*ca.* 2 Hz) by coupling to the NF_2 group.

About 0.5 ml of methylene chloride was added to the nonvolatile residue in the reaction tube; insoluble material remained. The predominant peak in the ^{19}F nmr of this solution was at ϕ −24.5. The entire residue was then partitioned between methylene chloride and water. A solid remained when the methylene chloride was evaporated; this solid was recrystallized from hexane and gave N-[1,1-bis(difluoramino)ethyl]acetamide (**45**), 0.21 g, mp 98–100°.

Anal. Calcd for $C_4H_7N_3F_4O$: C, 25.40; H, 3.73; N, 22.22; F, 40.2. Found: C, 25.71; H, 4.01; N, 21.26; F, 39.5.

The ^{19}F nmr spectrum showed a peak at ϕ −24.5. The ^1H nmr spectrum showed τ 7.83, sharp singlet of $CH_3C{=}O$ superimposed on quintuplet (about one-cycle coupling) of $CH_3C(NF_2)_2$ and broad absorption at τ 3.18 (–NH–).

Preparation of α,α-Bis(difluoramino)-α-chloro-4-bromotoluene (32).—A solution of 10 g of 1-(4-bromophenyl)-1-chloro-1-difluoramino-2-(fluorimino)propane (**6**) in 22 ml of methylene chloride was added to 15 ml of 30% fuming sulfuric acid over which 125 mmol of difluoramine was refluxing from a −80° condenser. After 2 hr at 10–25°, the excess difluoramine was vented in a nitrogen stream, and the residual solution, diluted with methylene chloride, was poured over ice. The organic layer was washed with water and aqueous sodium bicarbonate solution. The residue obtained upon evaporation of the methylene chloride was chromatographed on a silica gel column packed in pentane. Elution of the column with methylene chloride–pentane (1:19) gave **32**, 7.2 g, a colorless liquid.

Reaction of Difluoramine, Boron Trifluoride, and 1-Phenyl-1,1-bis(difluoramino)-2-(fluorimino)propane (35).—A mixture of 4 ml of methylene chloride, 1.00 g (4 mmol) of fluorimine **35**, 200 cc (STP) of difluoramine, and 120 cc (STP) of boron trifluoride in a Fischer–Porter pressure tube was stirred 30 min at ice-bath temperature and at ambient temperature for 1 hr. The tube was opened and the volatile materials were pumped off. The residue was partitioned between methylene chloride and water. The methylene chloride layer was separated, washed, and dried. The organic product was chromatographed on silica gel column packed in pentane–methylene chloride (50:1). Elution of the column with pentane–methylene chloride (15:1) gave a colorless liquid, 0.56 g, presumably 2-aza-1-fluoro-1-phenyl-3,3-bis(difluoramino)-1-butene [ϕ, $-CF{=}NC(NF_2)_2CH_3$], **50**.

Anal. Calcd for $C_9H_8N_3F_5$: C, 42.69; H, 3.18; N, 16.60; F, 37.5. Found: C, 42.49; H, 3.40; N, 17.33; F, 38.0.

The next fraction, 0.15 g, eluted from the column with methylene chloride, was N-[1,1-bis(difluoramino)ethyl]benzamide (**46**), mp 92–93° (from hexane).

Anal. Calcd for $C_9H_9N_3F_4O$: C, 43.03; H, 3.61; N, 16.73; F, 30.26. Found: C, 43.13; H, 3.91; N, 16.18; F, 29.4.

The ^{19}F nmr spectrum showed a doublet at ϕ −25.2, −24.8. The ^1H nmr spectrum showed τ 7.74 ($-CH_3$) and aromatic proton multiplets at τ 2.45 and 2.16.

The nmr spectrum of the residue before chromatography indicated that there was no change in product composition during chromatography.

Hydrolysis of 2-Aza-1-fluoro-1-phenyl-3,3-bis(difluoramino)-1-butene (50).—A solution of 136 mg of the azabutene **50** in 10 ml of methanol–water (1:1) was stirred at ambient temperature while 0.52 *N* sodium methoxide in methanol was added until the reaction mixture remained basic to pH paper for 10 min. Water was added to the methanolic solution, and the organic product was extracted into methylene chloride. Evaporation of the methylene chloride left a solid residue. One recrystallization of this residue from hexane gave N-[1,1-bis(difluoramino)ethyl]-benzamide (**46**), 82 mg, mp 91–92.5°. The infrared spectrum was identical with that of a sample isolated from the boron trifluoride reaction (above).

Hydrolysis of N-[1,1-Bis(difluoramino)ethyl]benzamide.—A mixture of 72 mg of the benzamide **46**, 2 ml of water, 2 ml of methanol, and 4 ml of 0.52 *N* sodium methoxide in methanol was refluxed 105 min. The solution was cooled, acidified, and poured into water. Extraction of the aqueous phase was carried out with methylene chloride. Benzoic acid, 26 mg, was obtained upon evaporation of the methylene chloride and was identified by infrared spectrum and mp 121–122° (from hexane). The aqueous washes contained 21 mg of fluoride ion; theoretical value for destruction of starting material is 22 mg.

Preparation of α,α,α-Tris(difluoramino)toluene (36).—1-Phenyl-1,1-bis(difluoramino)-2-(fluorimino)propane (**35**, 6 g), in 10 ml of methylene chloride was added to 12 ml of 30% fuming acid containing an excess of refluxing difluoramine. The mixture was stirred at 15–25° for 3 hr. Methylene chloride (100 ml) was added, and the acid layer was separated. The methylene chloride was washed with 10% aqueous sodium bicarbonate solution and water. A total of 1.69 g of benzoic acid was recovered from the acid layer and the aqueous washes. The residue remaining after the methylene chloride had distilled was fractionated *in vacuo* through −25 and −80° traps. The −25° trap retained α,α,α-tris(difluoramino)toluene (**36**), 0.3 g, a colorless liquid. The ^{19}F nmr spectrum showed single peak at ϕ −27.8. The ^1H nmr spectrum showed only an aromatic multiplet at τ 2.0–2.5.

The tristoluene **36** was also prepared as follows. A mixture of 4 ml of methylene chloride, 2 ml of fluorosulfonic acid, and 140 cc (STP) of difluoramine was stirred at −10° in a 200 ml, three-necked flask attached to a manometer. A solution of 1.0 g (3.1 mol) of 1,1-bis(difluoramino)-1-phenyl-2-(fluorimino)butane (**12**) in 4 ml of methylene chloride was added dropwise at −10°. The mixture was allowed to warm to 20° and was stirred for 1 hr. The excess difluoramine was quickly condensed off, methylene chloride was added to the residue, and ice water was added. The organic layer was separated as usual and concentrated to 2 ml by distillation. Distillation *in vacuo* through traps cooled to −45 and −80° gave, in the 45° fraction, α,α,α-tris(difluoramino)toluene, 0.14 g.

Reaction of 1,1-Bis(difluoramino)-2-(fluorimino)cyclohexane and Difluoramine.—A 5.3-g sample of the fluorimine **10** in 30 ml of 1,1,2-trichlorotrifluoroethane (Freon 113) was added to about 200 mmol of HNF_2 refluxing over 20 ml of fluorosulfonic acid. The temperature was at 5–11° during the addition, then was maintained at 14–16° for 150 min. The HNF_2 was vented and the residual solution was dumped on ice. The organic product was extracted with methylene chloride, the organic phase was washed with water, 5% aqueous sodium bicarbonate and again with water. The methylene chloride was removed at reduced pressure to leave 4.6 g of residue. This residue was chromatographed on a silica gel column packed in pentane–methylene chloride (20/1). The first material eluted, 0.32 g, had no ^{19}F nmr peak and was discarded. The second fraction, 0.12 g, had ^{19}F nmr peaks at ϕ −23.4 and +26.3, but was not examined further. The third fraction, eluted by 1:1 pentane–methylene chloride, 0.32 g, was 6,6,6-tris(difluoramino)hexanenitrile. The next fraction, eluted by methylene chloride, was 1-aza-2-fluorimino-3,3-bis(difluoramino)cycloheptane (**59**), 0.837 g. A sample was recrystallized from hexane, mp 75–77°.

Anal. Calcd for $C_6H_9N_4F_5$: C, 31.04; H, 3.91; N, 24.13; F, 40.9. Found: C, 30.98; H, 4.04; N, 23.10; F, 41.7.

The ^{19}F nmr spectrum showed peaks at ϕ −27.4 and −26.7 and ϕ +41.1 and +41.3 in CCl_4 solution. Addition of trifluoroacetic acid collapsed the upfield doublet to a singlet at ϕ +45.7. Heterodecoupling the ^{19}F peak at ϕ +41.2 also collapsed it to a singlet.

The next fraction from the column (2% ethyl acetate in methylene chloride) was amide **33**, 0.72 g, mp 70–71°.

This was followed by amide **58**, 0.56 g, mp 109–110°, eluted by 10% ethyl acetate in methylene chloride.

Anal. Calcd for $C_6H_9N_3F_4O$: C, 33.49; H, 4.22; N, 19.53; F, 35.3. Found: C, 33.61; H, 4.30; N, 19.26; F, 35.3.

The ^{19}F nmr spectrum showed a single peak at ϕ −26.5.

The last fraction was eluted by 10% methanol in methylene chloride and was 0.34 g of an oil. This was chromatographed on silicic acid and eluted with methylene chloride–acetone (9:1). The white solid was recrystallized from hexane to give 6,6,6-tris(difluoramino)hexanamide (**60**), mp 72–74°.

Anal. Calcd for $C_6H_{10}N_4F_6O$: C, 26.87; H, 3.76; N, 20.89; F, 42.5. Found: C, 26.75; H, 3.97; N, 20.79; F, 42.6.

The ^{19}F nmr spectrum showed a single peak at ϕ −27.7.

When a reaction was conducted as above, but in methylene chloride solution with a reaction time of 2 hr at −80 to 0°, the main nitrile cut was 6,6-bis(difluoramino)6-fluorosulfatohexanenitrile (**57**). It was purified by chromatography on silica gel; elution was successful with pentane–methylene chloride, 1:1.

Anal. Calcd for $C_6H_8N_3F_5SO_3$: C, 24.24; H, 2.71; N, 14.14. Found: C, 24.89; H, 3.50; N, 14.39.

The ^{19}F nmr spectrum showed single peaks at ϕ −48.3 and −25.6; ratio 1:4.

When a reaction with 5.0 g of fluorimine in 30 ml of methylene chloride (instead of Freon 113) as described above, the products isolated after silica gel chromatography were nitrile **39** (11%), amide **60** (5%), a mixture of amides **33** and **58** (total of 38%) and fluorimine **59** (5%).

Reaction of 1,1-Bis(difluoramino)-2-(fluorimino)cyclopentane and Difluoramine. A. With Fluorosulfonic Acid.—A solution of 2.5 g of the fluorimine **9** in 7 ml of methylene chloride was added to 400 mmol of difluoramine refluxing over 5 ml of methylene chloride and 3 ml of fluorosulfonic acid at −10°. The mixture was stirred at −5° for 1 hr. Excess difluoramine was vented and the residue was poured on ice and methylene chloride. The organic layer was washed with water, 5% aqueous sodium bicarbonate, and water. The methylene chloride was removed at reduced pressure, and after spectral samples had been removed, the residue was chromatographed on silica gel. Elution with 10:1 pentane–methylene chlorides gave 0.16 g of recovered **9**. Elution with the same solvents, 1:1, gave 5,5-bis(difluoramino)-5-fluorosulfatopentanenitrile (**71**), 0.59 g.

Anal. Calcd for $C_5H_6N_3F_5O_3S$: C, 21.21; H, 2.12; N, 14.84; F, 35.5. Found: C, 21.95; H, 2.42; N, 16.58; F, 34.4.

The ^{19}F nmr spectrum showed sharp peaks at ϕ −48.3 and −25.7; ratio 1:4. Continued elution of the column with methylene chloride gave 3,3-bis(difluoramino)-2-azacyclohexanone (**66**), 0.26 g, mp 140–142° (hexane).

Anal. Calcd for $C_5H_7N_3F_4O$: C, 29.85; H, 3.51; N, 20.89. Found: C, 29.86; H, 3.74; N, 20.85.

The ^{19}F nmr spectrum showed a peak at ϕ −23.9.

B. With Boron Trifluoride.—A mixture of 0.60 g of fluorimine **9**, 120 cc (STP) of difluoramine, 180 cc (STP) of boron trifluoride, and 2 ml of methylene chloride was stirred in a pressure tube at 0° for 30 min and at 20° for 90 min. The tube was vented *in vacuo*, and the residue portioned between methylene chloride and water. Evaporation of the methylene chloride left 0.45 g of residue. Chromatography of this residue over silica gel as usual gave, in the pentane–methylene chloride (2:1 and 1:1) eluates, a mixture of nitriles **24** and **38**, 0.10 g. A clean separation of these two nitriles could be obtained by vpc on a 5-ft Dow 710 silicon column at 125°. The fluorobis(difluoramino)nitrile **24** was eluted first (8-min retention time). The ^{19}F nmr spectrum showed peaks at ϕ −21.0 (NF_2) and +142.0 (CF); ratio 4:1. The tris(difluoramino)nitrile **38** had a retention time of 14 min.

Elution with methylene chloride gave amide **66**, 0.075 g. Elution with methylene chloride containing ethyl acetate (5–10%) gave N-(difluoramino)pyrrolidone (**67**), 0.120 g, a liquid.

Anal. Calcd for $C_5H_8N_2F_2O$: C, 40.00; H, 5.37; N, 18.66; F, 25.3. Found: C, 38.23; H, 5.76; N, 18.86; F, 24.3.

Spectral properties of **67** are reported in the Discussion.

Reaction of Paraformaldehyde, Difluoramine, and 2-Pyrrolidone.—Paraformaldehyde, 0.48 g, and difluoramine, 360 cc (STP), were allowed to interact overnight. The difluoramino methanol was then collected by distillation *in vacuo* into a −80° trap, and transferred to a U tube containing 1.7 g of 2-pyrrolidone, 12 ml of concentrated sulfuric acid, and 12 ml of 30% fuming sulfuric acid at −80°. The mixture was allowed to warm to ambient temperature and was stirred 1 hr. The mixture then was poured over ice, and partitioned between methylene chloride and water. Evaporation of the methylene chlorides gave a residue that had infrared, ^{19}F, and ^1H nmr spectra identical with those of **67**.

Reaction of 1,1-Bis(difluoramino)-2-(fluorimino)cycloheptane and Difluoramine.—To a refluxing mixture of 220 mmol of HNF_2 in 20 ml of fluorosulfonic acid and 10 ml of Freon 113 was added dropwise a solution of 5.0 g (0.0216 mol) of 1,1-bis(difluoramino)-2-(fluorimino)cycloheptane (**11**) in 20 ml Freon 113. The contents were allowed to stir for about 15 min at 16°. The contents were poured onto ice and extracted with 50 ml of Freon 113. The organic layer was washed with 5% $NaHCO_3$ solution, then water, and dried over $CaCl_2$. The Freon was removed on a rotary evaporator; the residue weighed 3.2 g. Another similar run was made except the time of the reaction was increased to 100 min. The yield of crude product was 2.80 g. The products were combined after inspection of their ^{19}F resonance spectra revealed the similarity of the two product mixtures.

The purification of the products was effected by chromatography through silica gel. The isolated fractions, in the order in which they were eluted, were 1.95 g of recovered 1,1-bis(difluoramino)-2-fluoriminocycloheptane and 1,1,2-tris(difluoramino)cycloheptane, 0.44 g of unknown compound, 0.89 g of tris(difluoramino)nitrile **40**, 0.19 g of amide **72**, and 0.78 g of amide **73**. These products were rechromatographed to obtain samples for elemental analyses.

Anal. for unknown compound (infrared peaks at 4.56 and 5.95 μ). Found: C, 31.42; H, 4.65; N, 19.83; F, 41.09.

The ^{19}F nmr spectrum showed peaks at ϕ −30.0 and −46.3; ratio 2:1. The ^1H nmr spectrum showed peaks centered at 255, 158, and 112 Hz downfield from TMS at 60 MHz, ratio 2:2:6.

Anal. Calcd for amide **72** (mp 85–87°), $C_7H_{11}N_3F_4O$: C, 36.70; H, 4.80; N, 18.35; F, 33.2. Found: C, 36.43; H, 4.95; N, 17.84; F, 32.17.

The ^{19}F nmr spectrum showed a peak at ϕ −29.7. The ^1H nmr spectrum showed τ 3.13 (NH), 6.42 ($-CH_2N$), 7.50 [$-CH_2C(NF_2)_2$] and 8.27 (ring CH_2); ratio 1:2:2:6.

Anal. Calcd for amide **73** (mp 71–73°), $C_7H_{11}N_3F_4O$: C, 36.70; H, 4.80; N, 18.35; F, 33.2. Found: C, 36.47; H, 4.97; N, 18.31; F, 33.19.

The ^{19}F nmr spectrum showed a peak at ϕ −24.0. The ^1H nmr spectrum showed two broad peaks, τ 7.30 and 8.32; ratio 2:3. The NH appeared to be at τ 2.85.

Registry No.—**1**, 20122-67-2; **2**, 16704-36-2; **3**, 20122-69-4; **4**, 20122-70-7; **5**, 20122-71-8; **6**, 20122-72-9; **7**, 20122-73-0; **8**, 20122-74-1; **9**, 20122-75-2; **10**, 20122-76-3; **11**, 20122-77-4; **12**, 20122-78-5; **13**, 20122-79-6; **14**, 20122-80-9; **15**, 20122-81-0; **23**, 20122-82-1; **26**, 19955-15-8; **27**, 20122-84-3; **28**, 19955-23-8; **29**, 20122-86-5; **30**, 20122-87-6; **31**, 20122-88-7; **32**, 20122-89-8; **33**, 20122-90-1; **36**, 20122-91-2; **37a**, 20122-92-3; **37b**, 20122-93-4; **38**, 20122-94-5; **39**, 201222-95-6; **45**, 20122-96-7; **46**, 20122-97-8; **47**, 20116-42-1; **53**, 20116-43-2; **54**, 20116-44-3; **57**, 20116-45-4; **58**, 20116-46-5; **59**, 20116-47-6; **60**, 20116-48-7; **66**, 20116-49-8; **67**, 20116-50-1; **71**, 20116-51-2; **72**, 20116-52-3; **73**, 20116-53-4; $CH_3C(NF_2)_3$, 20116-54-5; $CN(CH_2)_5C(NF_2)_3$, 20116-55-6; 1-fluoro-1-(*p*-methoxyphenyl)-2-aza-3,3-bis(difluoramino)-1-butene, 20116-56-7; N-[1,1-bis(difluoramino)-1-propyl]benzamide, 20116-57-8; N-[1,1-bis(difluoramino)ethyl]-*p*-chlorobenzamide, 20116-58-9; 2-chloro-2,3-bis(difluoramino)butane, 20116-40-9; 2-aza-1-fluoro-1-*p*-chlorophenyl-3,3-bis(difluoramino)-1-butene, 20116-41-0.

Acknowledgment.—This research was carried out during 1963–1965 for the Advanced Research Projects Agency under U. S. Army Missile Command, Contract DA-01-021-11909. The encouragement and contributions of Dr. J. P. Freeman aided greatly.

The Anomalous Chemiluminescence of Phthalic Hydrazide[1]

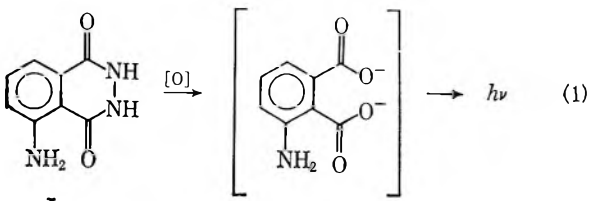
EMIL H. WHITE, DAVID F. ROSWELL, AND OLIVER C. ZAFIRIOU

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Received October 28, 1968

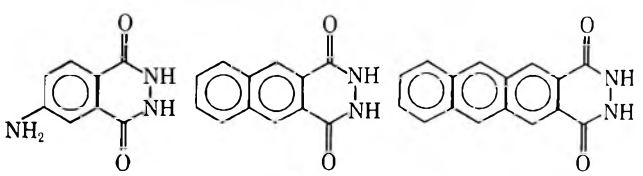
Phthalic hydrazide (VI), the simplest member of a series of chemiluminescent compounds that includes luminol (I), is chemiluminescent in aprotic solvents. Other members of this series emit *via* fluorescence from the corresponding phthalate ion with concentration-independent quantum yields. Phthalate ion itself is nonfluorescent, however, and the quantum yield of the emission at *ca.* 525 nm from phthalic hydrazide increases with the concentration of VI. The emission spectrum of the chemiluminescence matches the fluorescence of solutions of the monosodium salt of VI in aprotic solvents; these facts and other evidence suggest that the mononegative ion of phthalic hydrazide (VI) is the light emitter in this anomalous case of hydrazide chemiluminescence.

The chemiluminescence of luminol (I) involves the chemical production of excited 3-aminophthalate ion.



I II (1)

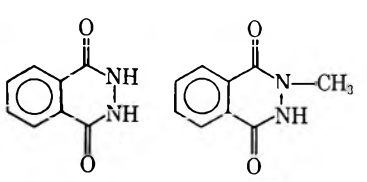
Fluorescence from II* is responsible for the light emission, and the ground-state 3-aminophthalate ion produced is the sole organic product of the reaction.[2] This reaction pathway—formation of an excited *o*-dicarboxylate ion, followed by fluorescence—also describes the chemiluminescence of other cyclic aromatic hydrazides which have been studied, such as isoluminol (III) and the unsubstituted hydrazides IV and V.[3] This scheme



III IV V

is applicable to hydrazide chemiluminescence carried out in either the "aqueous system" (hydrazide plus aqueous alkaline hydrogen peroxide and a peroxide-decomposing catalyst or oxidizing agent) or the "aprotic system" (hydrazide in an aprotic polar solvent plus oxygen and a strong base).[2]

The general scheme (eq 1) accounts for the chemiluminescence of all the hydrazides that have been examined with the exception of the "parent" hydrazide, 2,3-dihydrophthalazine-1,4-dione (VI). Although phthalate ion appears to be completely nonfluorescent, compound VI chemiluminesces in the aprotic system. Furthermore, the yellow chemiluminescence emission of VI (~525 nm) occurs at *longer* wavelengths than the emission from the more highly conjugated analogs IV (deep violet emission at ~360 nm) and V (blue emission at ~420 nm). The trend established by IV and V leads to the prediction that phthalic hydrazide (VI) should emit at very short wavelengths (~300 nm). We have studied the chemiluminescence of compound VI in order to clarify these discrepancies.



VI VII

Results

Samples of 2,3-dihydrophthalazine-1,4-dione from various sources were assayed for light production; no variation in the chemiluminescence was found. The infrared and ultraviolet spectra of the various samples were identical, and a sample carefully prepared from purified materials did not change in chemiluminescence or spectroscopic properties upon sublimation, crystallization from acetic acid, or crystallization of its monosodium salt from methanol–water.[4] All purified samples were homogeneous by paper chromatography. We therefore proceeded on the assumption that the chemiluminescence of VI is an intrinsic property, and not the result of impurities.

Preliminary observations revealed several important features of the chemiluminescent reaction. Colorless solutions of VI in dimethyl sulfoxide (DMSO) or hexamethylphosphoramide (HPT) became yellow when potassium *t*-butoxide was added, and these solutions fluoresced yellow. Both the fluorescence and the yellow color faded upon addition of small amounts of water and they returned when large amounts of the aprotic solvent were added. Solutions of the sodium salt of VI in DMSO or HPT are yellow, and they show the same behavior on dilution with water; paper chromatography of these solutions revealed only the presence of phthalic hydrazide. These oxygen-stable solutions of the monosodium salt of VI chemiluminesce yellow when excess potassium *t*-butoxide is added; during the reaction, a fine white precipitate appears (dipotassium phthalate) and the color eventually disappears.

A series of ultraviolet spectra of salts of VI and its N-methylated analog, VII, were taken in DMSO–water mixtures of varying composition. As shown in Table I, the absorption maxima of both compounds shift markedly to longer wavelengths as the proportion of water in

(1) Taken in part from the Doctoral Dissertations of O. C. Zafiriou and D. F. Roswell, The Johns Hopkins University.

(2) (a) E. H. White and M. M. Bursey, *J. Amer. Chem. Soc.*, **86**, 941 (1964); (b) E. H. White in "Light and Life," W. D. McElroy and B. Glass, Ed., Johns Hopkins Press, Baltimore, Md., 1961, p 183; (c) E. H. White, O. C. Zafiriou, H. M. Kägi, and J. H. M. Hill, *J. Amer. Chem. Soc.*, **86**, 940 (1964).

(3) (a) O. C. Zafiriou, unpublished work; (b) K. D. Gundermann and M. Drawert, *Chem Ber.*, **95**, 2018 (1962).

(4) A purification of phthalic hydrazide which removes a chemiluminescent impurity not found in our work has been reported: M. M. Rauhut, A. M. Semsel, and B. G. Roberts, *J. Org. Chem.*, **31**, 2431 (1966).

TABLE I

ABSORPTION SPECTRA OF THE MONOSODIUM SALTS OF VI AND VII

Solvent[a]	Absorption maximum[b] Salt of VI	Salt of VII
0.1 *N* KOH	310	313
DMSO–H_2O (9:1)[c]	342	345
DMSO–0.1 *N* KOH (9:1)[c]	342	345
DMSO–H_2O (100:1)[c]	360	365
DMSO–0.1 *N* KOH (100:1)[c]	360	365
DMSO[c]	364[d]	368[e]
DMSO–KO-*t*-Bu[c]	*f*	367

[a] Volume/volume. [b] Longest wavelength absorption band. [c] Solutions yellow owing to tailing into the visible region. [d] Log ϵ 3.55. [e] Log ϵ 3.56. [f] Oxidation occurs.

the solvent decreases. The shape and intensity of the long-wavelength band remains nearly constant, and there is no isosbestic point, or appearance of additional peaks.

The fluorescence spectra of the monosodium salt of phthalic hydrazide in HPT (Figure 1) and DMSO are shown in Table II; the excitation spectra are in good agreement with the absorption spectra determined in the same solvent. The chemiluminescence emission spectrum of a reacting solution of phthalic hydrazide in HPT containing *t*-butoxide ion, measured with a spectrophotofluorimeter, is compared in Figure 1 with the fluorescence of solutions of the mono sodium salt of phthalic hydrazide. It can be seen that the *fluorescence* of the mononegative ion of VI matches the chemiluminescence emission of VI. Relevant data for DMSO and HPT systems and for 4-methylphthalic hydrazide, which also exhibits this same identity of initial fluorescence and chemiluminescence spectral distributions, are presented in Table II.

TABLE II

FLUORESCENCE–CHEMILUMINESCENCE EMISSION WAVELENGTHS

Compound	Solvent	Emission maxima[a] Fluorescence	Chemiluminescence
Phthalic hydrazide (VI) monosodium salt	H_2O	467[c]	*c*
	DMSO	520	530
	HPT	525	525
N-Methylphthalic hydrazide (VII) monosodium salt	DMSO	515	
4-Methylphthalic hydrazide monosodium salt	HPT	526	522
Dipotassium phthalate[b]	H_2O	None[d]	
	DMSO	None	

[a] ±5 nm, uncorrected spectra. Extra base added to observe chemiluminescence. [b] This salt is very sparingly soluble in DMSO. [c] Extremely low intensity. [d] Phosphorescence has been detected in glasses at ~420 nm at 77°K.

The fluorescence quantum yield of dilute solutions of the salt of VI in HPT was determined to be 0.002 ± 0.001; the value for the N-methylated derivative VII is similar. The total amount of light emitted per mole of hydrazide VI that reacted was found to depend on the concentration of VI, as shown in Table III. The quantum yield of the chemiluminescence of 5×10^{-4} *M* VI was determined to be $\sim 3 \times 10^{-5}$ (photons/mole of VI reacted) by comparison with the known light yield of

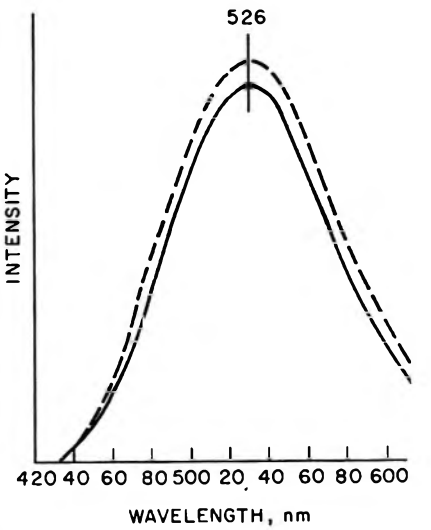


Figure 1.—The fluorescence (- - -) and chemiluminescence (—) spectra of the monosodium salt of phthalic hydrazide (VI).

luminol (I). Since these reactions are carried to completion, the quantum yields measured are average values reflecting the decrease of VI to zero during the reaction. In contrast to the concentration-dependent quantum yield of the chemiluminescence of VI, the fluorescence yield of the sodium salt of VI is constant (fluorescence intensity linearly related to concentration).

TABLE III

TOTAL LIGHT FROM VI *vs.* INITIAL CONCENTRATION

$10^4 \times$ [VI]	$10^6 \times$ coulombs[a]
10.0	22.8, 22.2
5.0	11.2, 12.1
4.0	8.1, 7.5
2.5	2.45, 2.15
1.25	0.55, 0.65

[a] Charge collected on capacitor. Values are linearly related to total light emission.

Efforts to alter either the emission spectrum or the quantum yield of the chemiluminescence by adding foreign fluorescers did not result in the appearance of new emission peaks or changes in the quantum yield (Table IV). Similarly, 1-methoxy-4-hydroxyphthazine had no effect on the reaction. Compound VII was shown to be fluorescent in the reaction medium, and stable to it for the duration of the experiments.

TABLE IV

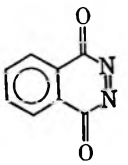
EFFECT OF ADDED FLUORESCERS ON THE CHEMILUMINESCENCE OF VI

Added fluorescer	$10^4 \times$ [fluorescer]	$10^4 \times$ [VI]	$10^6 \times$ coulombs[a]
None		2.02	1.45 ± 0.03
VII sodium salt	1.95	2.02	1.47 ± 0.03
None		1.75	1.20 ± 0.05
8-Aminonaphthalene-2-sulfonic acid	1.63	1.75	1.20 ± 0.05
Anthranilic acid	2.12	1.75	1.0[b]

[a] Charge collected on capacitor; values (average of duplicate determinations) are linearly related to total light emitted. [b] Solution colored at end of reaction.

The precipitate formed during the reaction is dipotassium phthalate, and only phthalic acid (and occasionally some VI) could be detected in the spent reaction solutions by paper chromatography. No fluorescence from phthalic acid, or its mono- and dinegative ions, could be detected in aqueous solution or in mixtures of water and DMSO. Sodium phthalate is too insoluble to be studied in anhydrous aprotic solvents, but quaternary ammonium salts soluble in these media were also found to be nonfluorescent; high concentrations were also nonfluorescent indicating that emission from phthalate eximers was not occurring.

The two-electron oxidation product of VI, phthalazine-1,4-dione, VIII,[5] is, *a priori*, a reasonable intermediate in the chemiluminescence of VI.[6] This compound reacts



VIII

rapidly with butadiene, even at −80°, to yield a Diels–Alder adduct. However, addition of butadiene to a chemiluminescing solution of VI neither decreases the light intensity nor yields detectable amounts of adduct[7] (presumably because of the high rate of reaction of VIII with peroxide ion). Compound VIII was prepared and isolated as a green solid at −80° and aliquots were treated in DMF at −40° with potassium superoxide, sodium peroxide, and *t*-BuOK in *t*-BuOH; the latter reagent yielded a weak flash of light. In contrast, compound VI chemiluminesces in this system for several minutes with an intensity comparable to that of the flash.

Discussion

The interpretation of low-yield chemiluminescence reactions in terms of molecular species is complicated by the possibility that efficient impurities cause the emission. However, in the present case the data strongly imply that the mononegative ion of phthalic hydrazide is an essential reactant and also the light emitter. The spectral, chromatographic, and chemiluminescence properties of samples do not depend on their origin or mode of purification. Furthermore, the absorption spectra of solutions of the sodium salt of phthalic hydrazide in HPT or DMSO are identical with the fluorescence excitation spectra of these solutions (Table II). Thus, the emitting species is linked to the major absorbing species in solution. The continuous shifts in the absorption spectra of these solutions with changing solvent composition (Table I) are caused by a change in solvation and not by the formation of new chemical species in DMSO solution, as shown by the continuous shift, the failure of the shape or intensity of the band to change markedly, and the absence of isosbestic points.[8]

This observed narrowing of the S^0–S^1 gap of the anions of VI and VII is expected to occur in media (such as DMSO) which solvate anions poorly, provided that the transition involves greater charge delocalization in the excited state than in the ground state; the spectrum of VII, the N-methyl analog of VI, rules out the possibility that dinegative ion formation is involved. The same medium effects which vary the S^0–S^1 gap in VI anion probably cause the great loss in fluorescence efficiency in aqueous solution (by shifting or reordering the levels responsible for nonradiative decay of its S^1 state, for example by narrowing the S^1–T gap and thereby enhancing intersystem crossing).[9] It is noteworthy that the quantum yield of chemiluminescence of VI in the aqueous peroxide system has been reported[10] to be 10^{-10}, five orders of magnitude lower than the optimum yield in the aprotic system. Since neither phthalate ion nor phthalic hydrazide anion is detectably fluorescent under these conditions, no effective means exists for emission of light in the water system.

The main features of the chemiluminescence of phthalic hydrazide require a new mechanism for light emission. The nonfluorescence of phthalate ion clearly indicates that it is not the emitter; thus the scheme common to other hydrazide chemiluminescence reactions is not operative. Furthermore, the identity of the fluorescence of the initial solutions of phthalic hydrazide sodium salt to the chemiluminescence emission spectrum strongly implies that a key feature of the mechanism is the formation of an excited species which transfers energy to the anion of phthalic hydrazide itself. We reject alternative mechanisms involving reaction products which are formed in an excited state having the same fluorescence properties as phthalic hydrazide anion. This latter mechanism requires that the similarity of the fluorescence of phthalic hydrazide anion to the chemiluminescence is fortuitous and that the hypothetical product is rapidly destroyed after it emits; furthermore, it offers no explanation for the observed concentration dependence of the light yield (*vide infra*). An energy transfer mechanism of the type given by eq 1–4 fits the

$$A \xrightarrow{k_1} B^* \quad (1)$$

$$B^* + A(S^0) \xrightarrow{k_2} B + A(S^1) \quad (2)$$

$$B^* \xrightarrow{k_3} B + \text{heat} \quad (3)$$

$$A(S^1) \xrightarrow{k_4} A(S^0) + \text{light} \quad (4)$$

data. An electronically excited product, B*, is formed from A in the slow step (eq 1) of the reaction. It transfers energy to the initially present fluorescer A, in a bimolecular reaction (eq 2), and it also undergoes competing unimolecular (or pseudounimolecular) deactivation (eq 3). Since the energy transfer and the decay processes are of first and zero kinetic orders, respectively, the fraction of B* which excites the emitter, A, $[k_2A/(k_2A + k_3)]$ is concentration dependent. The linear plot of apparent quantum yield *vs.* initial concentration of A (Figure 2) fits this expression if $k_3 \gg k_2A$. This linearity implies that even at the higher concentrations studied most of the B* is deactivated. This prediction

(5) T. J. Kealy, *J. Amer. Chem. Soc.*, **84**, 966 (1962).

(6) (a) H. O. Albrecht, *Z. Phys. Chem.*, **A136**, 321 (1928); (b) H. Kautsky and K. H. Kaiser, *Z. Naturforsch.*, **5b**, 353 (1950); (c) E. H. White, E. G. Nash, D. R. Roberts, and O. C. Zafiriou, *J. Amer. Chem. Soc.*, **90**, 5932 (1968).

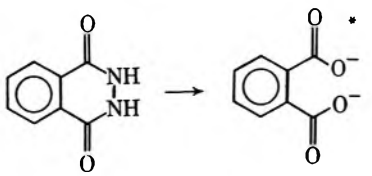
(7) A similar result has also been reported by Y. Omote, T. Miyake, and N. Sugiyama [*Bull. Chem. Soc. Jap.*, **40**, 2446 (1967)].

(8) H. H. Jaffé and Milton Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York, N. Y., 1966, Chapter 9.

(9) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 27–29.

(10) J Stauff and G. Hartmann, *Ber. Bunsinges. Phys. Chem.*, **69**, 145 (1965).

is consistent with the observation that the fluorescence quantum yield of phthalic hydrazide anion is *ca.* 100 times greater than the observed chemiluminescence quantum yield at the highest concentration studied. The results indicate that reaction 1 must produce B* in a yield of at least several per cent.[11] Since VI is the source of chemiluminescence in this system and phthalate ion is the reaction product, the chemical reaction leading to the primary excited state is probably analogous to that of other hydrazides.[2a,3a]



VI

Thus, the nonfluorescence of phthalate ion and the availability of a fluorescent acceptor of the electronic energy of excited phthalate would appear to account for the anomalous behavior of VI. However, the failure of added fluorescers to compete with the anion of VI in intercepting the primary excited state (Table IV) compromises this simple mechanism. Particularly striking is the inability of added VII to enhance the quantum yield; the structural and spectral similarities of the anions of VII and VI (Table I) imply that they are interchangeable if either an exchange or a dipole–dipole interaction energy transfer mechanism is involved.[12] Also important is the nonfluorescence of phthalate ion, which indicates a short lifetime for its excited singlet state;[13] a short-lived singlet is not expected to transfer to an acceptor ($<5 \times 10^{-4}$ *M*) with the required 1–2% efficiency by normal pathways. Finally, attempts to detect appreciable direct energy transfer from phthalate ion to the mononegative ion of VI in DMSO have been unsuccessful. Not much weight can be attached to this result, however, because of serious experimental difficulties, chief of which is the lack of a suitable "window" for irradiating phthalate ion in the presence of VI. This necessitates using high concentrations of phthalate ion (*ca.* 10^{-2} *M*) and at this concentration self-quenching will be serious, especially for triplet states.

The experimental results could be accounted for if the energy transfer were facilitated by hydrogen bonding between excited phthalate ion and the acceptor.[14] The substitute acceptor VII in its anionic form could not function as a hydrogen-bond donor, and hydrogen-bonding acceptors would be restricted to a narrow range of acidities ($pK_a \sim 13$), since stronger acids would react fully with potassium *t*-butoxide, and much weaker acids would not give sufficiently strong hydrogen bonds to permit energy transfer. Strong support for this idea comes from the observation that small amounts of potassium *t*-butoxide added to VI in DMSO lead to light emission, whereas large amounts lead to a quenching of the light emission. Presumably in the latter case, all of VI is converted into the dinegative ion and hydrogen

(11) The arguments presented in this paragraph do not depend on the assignment of molecular structure to the species involved; these considerations apply even in the unlikely event that an impurity is responsible for the chemiluminescence.

(12) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 5.

(13) See ref 12, pp 48–50.

(14) This possibility was suggested to us by Dr. N. J. Turro.

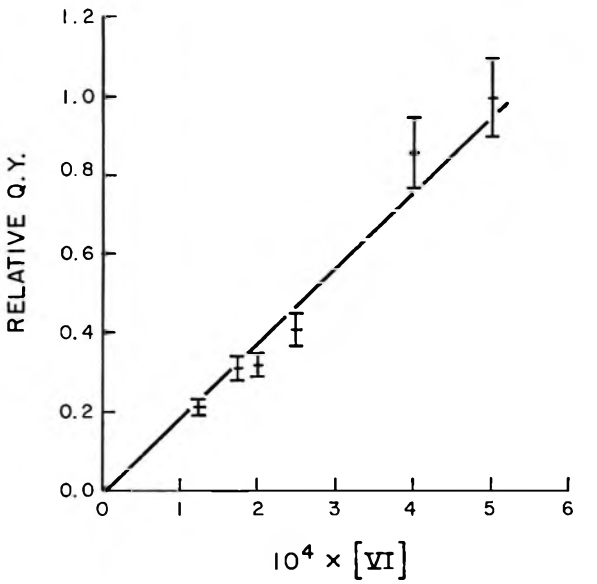
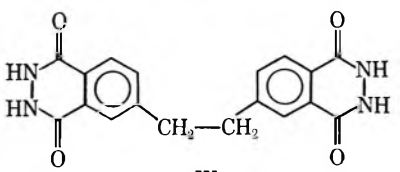


Figure 2.—Relative chemiluminescence quantum yield of phthalic hydrazide (VI) *vs.* initial concentration of VI.

bonding to the excited-state product (phthalate ion) is thus impossible. Further, if *t*-butyl alcohol or traces of water are added to these dark solutions containing an excess of potassium *t*-butoxide, the chemiluminescence emission returns to its former level, presumably because of the regeneration of the mononegative ion of VI. This effect of butoxide ion on the chemiluminescence of VI is far greater than the effect of butoxide ion on the fluorescence yield of the anion of VI.

Compound IX was synthesized in the hope that proximity would enhance the probability of transfer. However, IX is no more efficient than phthalic hydrazide.



IX

Since intramolecular hydrogen bonding is prohibited in IX and the relative orientations of the donor and acceptor are restricted, this result is inconclusive.

An alternative approach to the difficulties posed by the excited phthalate mechanism is the hypothesis that the uniqueness of the chemiluminescence of VI lies in the chemistry. A mechanism which has been proposed for luminol[6a,b] would in this case provide for the transfer of chemical energy in a step which yields excited VI anion directly, as shown in Figure 3. Since both diimide and the azaquinone required should have very short lifetimes under the conditions, this mechanism might account for the observed concentration dependence of the light yield and for the inability of VII to substitute for VI. However, it has been conclusively demonstrated that this mechanism is not operative for either hydrazide I[2a,b] or IV,[6c] and our experiments with the azaquinine VIII show that this compound leads to only weak chemiluminescence; a much brighter flash would be required to yield an amount of light comparable with that emitted by similar amounts of VI over a much longer time span. Furthermore, the generation of dimide in chemiluminescing solutions of VI in DMSO–*t*-butoxide

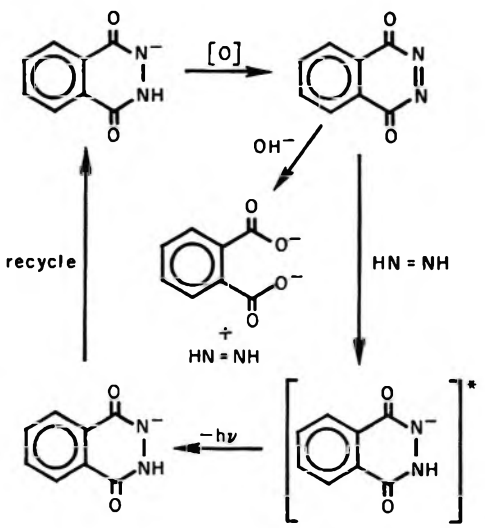
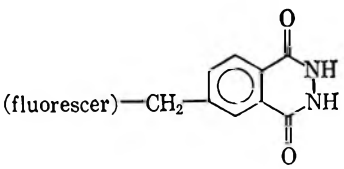


Figure 3.—Alternative mechanism for the chemiluminescence of phthalic hydrazide.

did not lead to an enhancement of the light level, but actually a decrease. Sources used were *p*-toluenesulfonic hydrazide,[15a] chloroacetic hydrazide,[15b] and hydrazine–copper mixtures.[15c,16]

This rejection of a chemical mechanism of energy transfer again indicates the involvement of an electronic energy transfer step which possesses some unusually selective feature. Recently it has been suggested[17a] that the chemiluminescence of donor–acceptor compounds, X, utilizing phthalic hydrazide as the energy



X

source, involves triplet–singlet energy transfer.[17b] This scheme predicts reasonably well the relative efficiency

donor (T^1) + acceptor (S^0) ⟶ donor (S^0) + acceptor (S^1)

of a hydrazide X in terms of the overlap between the long-wavelength absorption band of the acceptor and the phosphorescence of phthalate ion. The spin-forbidden nature[18] of this process makes it particularly susceptible to competition from allowed processes, and differences in these relative rates[19] may account for the unusual features of phthalic hydrazide energy transfer.

In conclusion, it appears that the chemiluminescence of phthalic hydrazide (VI) in DMSO and in HPT involves the formation of the mononegative ion of VI in an excited state; the mechanism whereby the chemical energy of oxidation is converted into the excitation energy of the hydrazide has not been established with certainty, but it appears reasonably certain that intramolecular energy transfer is occurring within a hydrogen-bonded complex from excited phthalate ion to the mononegative ion of VI.

(15) (a) S. Hünig, H. R. Müller, and W. Thier, *Tetrahedron Lett.*, 353 (1961); (b) R. Buyle, A. Van Overstraeten, and F. Eloy, *Chem. Ind.* (London), 839 (1964); (c) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Lett.*, 347 (1961).

(16) Lastly, attempts to detect a radical ion mechanism [D. M. Hercules, R. C. Lansbury, and D. K. Roe, *J. Amer. Chem. Soc.*, **88**, 4578 (1966); E. A. Chandross, J. W. Longworth, and R. E. Visco, *ibid.*, **87**, 3259 (1965)] by light emission during the electrolysis of a mixture of VI and potassium *t*-butoxide in DMSO were unsuccessful.

(17) (a) E. H. White, D. R. Roberts, and D. F. Roswell in Proceedings of the International Conference on Molecular Luminescence, Chicago, Ill., Aug 1968, E. C. Lim, Ed., W. A. Benjamin, Inc., New York, N. Y., 1968; (b) V. L. Ermolaev and E. B. Sveshnikova, *Opt. Spectrosc.* (USSR), **16**, 320 (1964).

(18) R. G. Bennett, R. P. Schwenker, and R. E. Kellogg, *J. Chem. Phys.*, **41**, 3040 (1964).

(19) E. F. Ullman and N. Baumann, *J. Amer. Chem. Soc.*, **90**, 4158 (1968).

Experimental Section

I. Methods.—Melting points were taken with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed either by Mr. Joseph Walters or by Galbraith Laboratories (Knoxville, Tenn.). Paper chromatography was performed in the descending manner using prewashed Whatman paper (No. 1 or No. 3MM). The eluent was 95% ethanol–water–concentrated ammonium hydroxide, 8:1:1. Spots were detected by long- and short-wavelength ultraviolet light and by spraying with either 0.1% methyl red in ethanol or 0.1% acridine in ethanol.

Infrared spectra were determined on either Model 137 or 337 Perkin-Elmer instruments. Ultraviolet and visible spectra were determined on a Cary Model 14 instrument and proton magnetic resonance spectra (nmr) were determined on a Varian Associates A-60 instrument. Chemical shifts are reported in τ units relative to internal tetramethylsilane (TMS).

Chemical screening experiments were performed in a dark room after dark adaption of the eye, and were witnessed by a second observer. Chemiluminescence relative efficiencies were determined using either RCA IP21 or IP28 phototubes, biased by a Fluke Model 4128 dc power supply. The output of the phototube was amplified with a unit designed and built by Mr. John Veise (Department of Biochemistry, The Johns Hopkins University). The amplifier signal was collected on a capacitor and recorded for total light yields, reported as coulombs per micromole at 700-V phototube bias.

Fluorescence and chemiluminescence emission spectra were determined on Aminco–Bowman spectrophotofluorimeters and recorded on a Houston Instrument Co. HR-96T X-Y recorder. Many of these spectra were rerun on a Hitachi Model MPF-2A recording spectrophotofluorimeter. Spectra are not corrected for phototube sensitivity, instrumental distortion, or source intensity fluctuation. Wavelengths were determined by superposition of a low-pressure mercury arc spectrum (Pen-Ray Lamp) on the recorded spectrum. Reported maxima are reproducible to within ±3 nm.

II. Materials.—Anthranilic acid, 8-aminonaphthalene-2-sulfonic acid, and 3-aminophthalic acid were commercial materials, homogeneous by paper chromatography. Potassium *t*-butoxide (MSA Research Corp.) was used as received. Dimethyl sulfoxide (Matheson Coleman and Bell) and hexamethylphosphoramide (Eastman) were each stirred overnight over crushed potassium hydroxide, decanted, and distilled from potassium *t*-butoxide. Distillations were performed with grease-free joints under oil pump vacuum (less than 1 torr) and at temperatures from 30 to 60°. A center cut of about 80% of the material was used.

2,3-Dihydrophthalazine-1,4-dione (VI). A.—Phthalic anhydride was prepared by heating an intimate mixture of potassium acid phthalate (Malinckrodt "Primary Standard," Lot No. 6074, 5 g) and potassium bisulfate (Merck "Reagent Grade," 20 g) to 150° in a large sublimation apparatus for 3 hr. A slow stream of dry nitrogen was swept through the apparatus. Phthalic anhydride sublimed in long needles; after 3 hr, 1 g was collected and stored in a desiccator over silica gel. A sample possessed sharp ir absorptions (chloroform) at 1855, 1810, 1790, 1775, 1450, and 1260 cm^{-1}.

B.—Reagent grade acetic acid was purified by the method of Fieser (distillation from potassium permanganate).[20]

C.—Hydrazine, 95%, was purified by distillation of commerical material at aspirator pressure. A central cut was used immediately.

D.—2,3-Dihydrophthalazine-1,4-dione was prepared from A, B, and C. Phthalic anhydride (0.50 g, 3.4 mmol) and acetic

(20) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 281.

acid (25 ml) were placed in a Carius tube under a nitrogen stream, and hydrazine (220 mg, 6.6 mmol) was added. The tube was degassed by two freeze–thaw cycles and sealed under vacuum. It was heated at 140° for 2 hr and then allowed to cool. The white crystals which formed were filtered off on a sintered-glass funnel, washed three times with acetic acid, and dried for 2 hr at 0.005-mm pressure: infrared (KBr) 3450, 3170, 3030, 2900 (all broad), and 1660, 1500, 1380, 1350, 1330, 1310, 1265, 1080, 795, 780, 685, and 630 cm^{-1}.

2-Methyl-2,3-dihydrophthalazine-1,4-dione (VII).—Methyl hydrazine (4.6 g, 0.10 mol) was added to phthalic anhydride (10 g, 0.0675 mol) in 150 ml of acetic acid and the mixture was refluxed for 2 hr. The cooled mixture was poured into 150 cc of water and filtered. The solid was washed with water and crystallized from water–acetic acid (1:1): mp 238.5–240° (lit.[21a] mp 239–240°); ir (KBr) 3400 (broad), 3100 (broad), 1645, 1625, 1590, and 1575 cm^{-1}.

1-Methoxy-4-hydroxyphthalazine was prepared by the method of Rowe and Peters:[21a] mp 189–190° (lit. mp 188°,[21a] 189°[21b]).

Dimethyl 4-Methylphthalate.—Fischer esterification (HCl–methanol) of 4-methylphthalic anhydride (20 g, 0.12 mol) yielded the corresponding dimethyl ester. Distillation at 150° (*ca.* 1 torr) gave 21.5 g (0.10 mol, 83%) of a clear liquid: infrared (neat) 1730, 1610, 1470 and 1290 cm^{-1}; nmr (CCL_4) τ 2.3–2.9 (3.02 H, multiplet), 6.19 (6.08, H singlet), 7.61 (3.00 H, singlet) [lit.[22] bp 147–151° (9 torr)].

6-Methyl-2,3-dihydrophthalazine-1,4-dione.—4-Methyl phthalic anhydride (1.62 g, 0.01 mol) was dissolved in glacial acetic acid (20 ml) and heated at 90° with hydrazine hydrate (3.0 g, 0.06 mol) until the solution turned turbid and then refluxed 1 hr, cooled, and filtered. The solid was dissolved in dilute aqueous potassium hydroxide, and precipitated with dilute acetic acid. Sublimation at 200–220° (1 torr) yielded 4-methylphthalic hydrazide: mp >350°; ir (KBr) 3200 (broad) and 1720 cm^{-1}.

Hydrazide Sodium Salts.—The hydrazide (10 mmol) was dispersed in 25 cc of water and 10 cc (10 mmol) of 1.00 *N* sodium hydroxide solution was added rapidly. After this solution became homogeneous, a small amount of 95% ethanol was added to precipitate the salt. The precipitate was filtered, washed with 95% ethanol, and dried *in vacuo*. These materials dissolved in water to give a solution of pH 8–9.

5-Amino-2,3-dihydrophthalazine-1,4-dione (Luminol) (I).—Powdered luminol was purified and isolated as the hydrobromide by crystallization from hot hydrobromic acid.

Phthalic Acid.—Solutions of phthalic acid in water were prepared by dissolving potassium acid phthalate (Malinckrodt "Primary Standard," Lot No. 6704) in aqueous hydrochloric acid.

Trimethylbenzylammonium Salt of Phthalic Hydrazide.—Phthalic hydrazide (*ca.* 1 g) was suspended in 10 ml of methanol, and "Triton B" (40% in methanol) was added dropwise with agitation until an aliquot diluted with water was strongly basic. After all of the material dissolved, the solution was evaporated to a thick glass, and the material was purified by crystallization from acetonitrile: mp 162–164.5° dec; nmr in D_2O (δ from sodium 2,2-dimethyl-2-silapentane-5-sulfonate; singlets at 3.27, 4.59, and 7.78, and a multiplet centered at 8.39 with the relative weightings 9/2/5/4).

Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80. Found: C, 69.13; H, 7.16.

Bis(trimethylbenzylammonium) Phthalate.—Phthalic acid (*ca.* 2 g) was suspended in 20 ml of methanol, and "Triton B" (40% in methanol) was added dropwise until all the material dissolved and a drop of the solution, on dilution to *ca.* 1 ml with water, was strongly basic (pH 11–12). The solution was concentrated to a thick oil, further concentrated under high vacuum, and crystallized three times from acetonitrile: mp 186–189° dec; nmr in D_2O (δ from sodium 2,2-dimethyl-2-silapentane-5-sulfonate; singlets at 3.22, 4.67, and 7.96, and a multiplet at *ca.* 7.92.

Anal. Calcd for $C_{28}H_{36}N_2O_4 \cdot H_2O$: C, 69.68; H, 7.94. Found: C, 70.18; H, 8.03.

Dipotassium, Disodium, and Dicesium Phthalate.—Stirred suspensions of phthalic acid water were titrated to pH 9 (pHydrion paper) with aqueous solutions of metal hydroxide and freeze dried. The salts were crystallized from methanol and dried *in vacuo* at 50°.

Phthalazine-1,4-dione (VIII).—The method of Kealy[5] was used to prepare VIII after stirring 3 hr at −45° the emerald green solution was filtered through a sintered disk at −80°. The filtrate was rapidly transferred (in a drybox) to a cold flask, which was connected to a diffusion pump. The solution was evaporated by pumping for 10 hr at −80° with continuous stirring; a bright green solid remained. About 10% of the solid was redissolved in cold acetone and treated with butadiene. Evaporation of the solvent left a crystalline white adduct (12.6 mg): mp 264–268° dec (lit.[5] mp 263–268° dec); nmr ($DCCl_3$) τ 1.80 (m, 2.1 H), 3.83 (broad s, 1.0), 5.30 (broad s, 3.1). The adduct weight indicates a 70% yield of VIII.

Dimethyl 4-Bromomethylphthalate.—Dimethyl 4-methylphthalate (6.5 g, 29 mmol) was dissolved in 100 cc of carbon tetrachloride and 5.5 g (30 mmol) of N-bromosuccinimide was added. The reaction mixture was irradiated under reflux with a sun lamp (GE 275 W) for 45 min. The succinimide was filtered, and the carbon tetrachloride was removed *in vacuo* to give a yellow oil; the nmr spectrum of this material indicated 60% bromination. Distillation gave one fraction (150–160°, 0.1 torr) of a clear liquid which on crystallization from ether–pentane gave a total of 3.65 g (12.5 mmol, 44%) of white crystals: mp 49–51°; infrared (KBr) 1720, 1600 and 1425 cm^{-1}; nmr ($CDCl_3$) τ 2.1–2.5 (3.00 H, multiplet), 5.50 (1.97 H, singlet), 6.08 (6.08 H, singlet).

Anal. Calcd for $C_{11}H_{11}O_4Br$: C, 44.45; H, 3.70. Found: C, 44.37; H, 3.81.

Triphenyl-3,4-dicarbomethoxybenzylphosphonium Bromide.—Triphenylphosphine (2.25 g, 8.6 mmol) and dimethyl-4-bromomethylphthalate (2.5 g, 8.4 mmol) were heated in 50 cc of benzene at reflux for 8 hr. After standing overnight the white crystalline precipitate was filtered and washed with two portions of dry benzene. A total of 4.2 g (7.5 mmol, 89%) of product was isolated: dec >150°; infrared (KBr) 1715, 1425 and 1370 cm^{-1}.

***cis*- and *trans*-1,2-Bis(3,4-dicarbomethoxyphenyl)ethylene.**—Triphenyl-3,4-dicarbomethoxybenzylphosphonium bromide (1.58 g, 3.0 mmol) was dissolved in 25 cc of methanol (distilled from magnesium turnings) and to this solution 8.1 cc of 0.37 *N* sodium methoxide (3.0 mmol) in methanol was added. This reaction mixture was stirred under nitrogen for 15 min and then 0.63 g (3.0 mmol) of 4-formyldimethylphthalate in 10 cc of methanol was added. After stirring for 10 min, a precipitate appeared, which when filtered off gave 0.30 g (0.73 mmol, 24%) of white material shown to be the pure *trans*-tetracarbomethoxystilbene. Crystallization from a chloroform–ether mixture gave translucent needles: mp 134–135°; infrared (KBr) 1720, 1605 and 1445 cm^{-1}; nmr ($CDCl_3$) τ 2.1–2.4 (2.96 H, multiplet), 2.80 (0.96 H, singlet), 6.03 (6.00 H, singlet); ultraviolet (C_2H_5OH) 328 mμ (log ϵ 4.48) and 235 (4.11).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 63.98; H, 4.96.

The methanol filtrate was evaporated to dryness *in vacuo* and extracted with hot ether. The ether extract, containing the *cis*-tetracarbomethoxystilbene as well as some triphenylphosphine oxide, was chromatographed on 20 g of silica gel with chloroform as the eluent. The initial fractions contained 0.8 g (20 mmol, 64%) of colorless oil which when crystallized from ether–pentane gave pure *cis*-tetracarbomethoxystilbene as white needles: mp 71–72.5°; infrared (KBr) 1720, 1595 and 1430 cm^{-1}; nmr ($CDCl_3$) τ 2.1–2.8 (3.12 H, multiplet), 3.25 (0.90 H, singlet), 6.08 (6.00 H, singlet); ultraviolet (C_2H_5OH) 300 mμ (log ϵ 4.25) and 235 (4.49).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 64.03; H, 4.89.

1,2-Bis(3′,4′-dicarbomethoxyphenyl)ethane.—*cis*-Tetracarbomethoxystilbene (85 mg, 0.19 mmol) in 20 cc of methanol was stirred with 30 mg of 10% palladium-charcoal under an atmosphere of hydrogen for 4 hr. The catalyst was then filtered off and the methanol was evaporated. Crystallization of the crude product from anhydrous ether gave 71 mg (0.17 mmol, 84%) of white crystals: mp 114–115°; infrared (KBr) 1740 cm^{-1}; nmr ($CDCl_3$) τ 2.2–2.8 (3.00 H, multiplet), 6.08 (5.91 H, two almost superimposed singlets), 7.00 (1.97 H, singlet).

Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.53; H, 5.20.

Subjecting the *trans*-tetracarbomethoxystilbene to the above procedure gave material identical in all respects with that obtained from the *cis* starting material.

(21) (a) F. Rowe and J. J. Peters, *J. Chem. Soc.*, 1331 (1933); (b) J. A. Elvidge and A. P. Redman, *ibid.*, 1710 (1960).

(22) K. Alder, R. Munders, W. Krane, and P. Wirtz, *Ann. Chem.*, **624**, 59 (1959).

1,2-Bis(6′,2′,3′-dihydro-1′,4′-diketophthalazyl)ethane.—1,2-Bis(3,4-dicarbomethoxyphenyl)ethane (130 mg, 0.31 mmol) was added to 5 cc of ethanol containing 0.5 cc of 95% hydrazine. This solution was degassed and sealed, and heated in a steam bath for 2.5 hr. The white crystalline product was filtered off, washed with ethanol, and triturated with boiling glacial acetic acid to give 115 mg (0.30 mmol, 96%) of white material: mp >300°; infrared (KBr) 1650, 1610, and 1400 cm^{-1}; ultraviolet (in hexamethylphosphoramide) 312 mμ (log ε 4.02). Paper chromatography on Whatman No. 1 paper showed one spot, R_f 0.32.

Anal. Calcd for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.03; N, 15.99. Found: C, 60.05; H, 4.20; N, 15.19.

A portion of the material was sublimed with a cool flame under high vacuum.

Anal. Found: C, 61.53; H, 4.21; N, 15.85.

Total Light Emission Studies.—A sample of the hydrazide solution, including any additives, was added to the cell of the light detector–integrator described. The cell was placed in the light-tight compartment, and *ca.* 50 mg of dry, solid potassium *t*-butoxide was added through a light-tight port with the phototube in operation, and the samples, agitated by a small magnetic stirrer bar, were monitored until no further light output occurred; additional butoxide was then added to ascertain that the reaction was complete.

Chemiluminescence Spectral Distribution Studies.—Chemiluminescence spectral distribution was determined by scanning samples in the spectrophotofluorimeter, using no exciting light. Samples were prepared as were the total light emission samples, except that oxygen and agitation was provided *via* air introduced into the cell through a long syringe needle. Two methods were used to ascertain that intensity decay during scan was not distorting curves.

(1) The sample was rescanned after the elapse of several scan times; curves were accepted if the intensity drop between successive scans was <20% at peak maximum.

(2) The Aminco–Bowman spectrometer was modified so that two phototubes monitored the emission, one before and one after emitted light was dispersed.

The "total light monitor" phototube output was time synchronized with the "dispersed light monitor" *via* an electrical marker signal. The total light decay curve was used to correct the dispersed curve for intensity–decay distortion.

Quantum Yield Determinations.—The chemiluminescence quantum yield of 5×10^{-4} *M* VI in HPT was determined to be $\sim 3 \times 10^{-5}$ by comparison of total light yields relative to luminol, I.[23] The relative total light yields were normalized for phototube sensitivity at the wavelength emission maxima.

The fluorescence quantum yield of the sodium salt of VI in HPT was determined by a comparison with D-luciferin in aqueous solution at pH 4.8. The fluorescence measurements were performed by Dr. T. A. Hopkins (Department of Biochemistry, The Johns Hopkins University) using a 150-W xenon arc, a Perkin-Elmer Corp. Model 98 monochromator, and a W. Fastie-type spectrophotometer. This spectrophotometer contained an EMI 9558 phototube with known spectral response in the region of interest (500–580 nm). Excitation of the samples was at 360 nm and the areas under the corrected emission curves were compared. From the known fluorescence quantum yield of 0.25 for D-luciferin,[24] the fluorescence quantum yield for the sodium salt of VI was calculated to be 0.002 ± 0.001.

Registry No.—VI, 1445-69-8; VI (Na salt), 20116-60-3; VI (trimethylbenzylammonium salt), 20116-61-4; VII, 18393-54-9; VII (Na salt), 20116-63-6; VIII, 20116-64-7; dimethyl 4-methylphthalate, 20116-65-8; 6-methyl-2,3-dihydrophthalazine-1,4-dione, 20116-66-9; bis(trimethylbenzylammonium) phthalate, 20116-39-6; dimethyl 4-bromomethylphthalate, 20116-67-0; triphenyl-3,4-dicarbomethoxybenzylphosphonium bromide, 20116-68-1; *cis*-1,2-bis(3,4-dicarbomethoxyphenyl)ethylene, 20122-46-7; *trans*-1,2-bis(3,4-dicarbomethoxyphenyl)ethylene, 20122-47-8; 1,2-bis(3′,4′-dicarbomethoxyphenyl)ethane, 20116-69-2; 1,2-bis(6′-2′,3′-dihydro-1′,4′-diketophthalazyl)ethane, 20116-70-5; 4-methylphthalic hydrazide (Na salt), 20116-71-6.

Acknowledgment.—We thank Dr. Thomas A. Hopkins for measuring the quantum yield of fluorescence of the monosodium salt of phthalic hydrazide. This investigation was supported by Public Health Service Research Grant No. NB 07868 of the National Institute of Neurological Diseases and Blindness.

(23) J. Lee, A. S. Wesley, J. F. Ferguson, III, and H. H. Seliger in "Bioluminescence in Progress," F. H. Johnson and Y. Haneda, Ed., 1st ed, Princeton University Press, Princeton, N. J., 1966, p 35.

(24) A. R. Morton, T. A. Hopkins, and H. H. Seliger, *Biochemistry*, **8**, 1598 (1969).

Thermal and Photochemical Addition Reactions of Organosilicon Hydrides

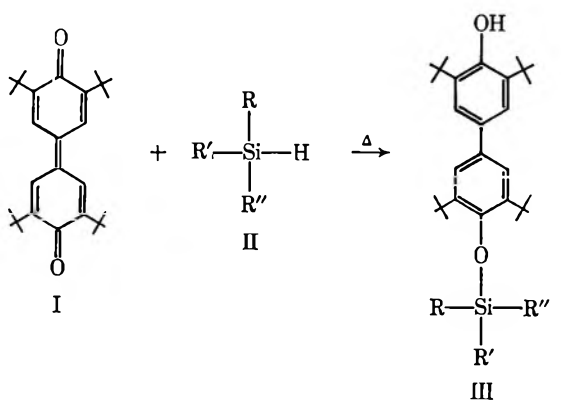
HANS-DIETER BECKER

General Electric Research and Development Center, Schenectady, New York 12301

Received October 3, 1968

Phenylsilicon hydrides react with benzophenone at elevated temperature, yielding alkoxysilicon compounds by 1,2 addition to the carbonyl group.[1] The addition of organosilicon hydrides to quinones, however, apparently has not been reported yet. Therefore, and in view of a recent report[2] on the thermal dehydrogenation of diphenylmethane by 3,3′,5,5′-tetra-*t*-butyldiphenoquinone (I), it appeared interesting to study the reaction of tetra-*t*-butyldiphenoquinone with some phenylsilicon hydrides.

We have now found that diphenylsilane (IIa) upon heating to 275° smoothly reacts with 3,3′,5,5′-tetra-*t*-butyldiphenoquinone to give the monodiphenylsilyl ether of 4,4′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl (IIIa) in 80% yield. Triphenylsilane and tribenzylsilane add to the diphenoquinone I in the same manner,



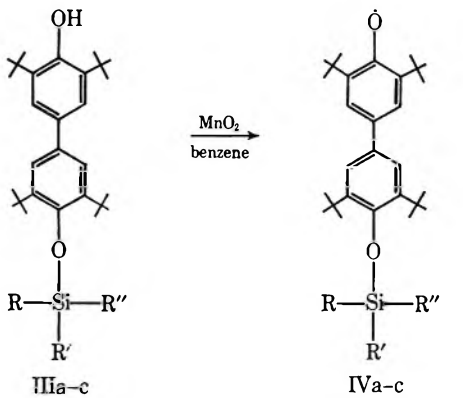
I + II → III

IIa and IIIa, R = H; R′ = C_6H_5; R″ = C_6H_5
IIb and IIIb, R = C_6H_5; R′ = C_6H_5; R″ = C_6H_5
IIc and IIIc, R = $C_6H_5CH_2$; $C_6H_5CH_2$; $C_6H_5CH_2$

giving the monosilyl ethers IIIb and IIIc in 69 and 30% yield, respectively.

The structure of the addition products III is confirmed by analytical and nuclear magnetic resonance (nmr) spectroscopic data. Figure 1 shows the increasing effect of magnetic shielding of one pair of *t*-butyl groups due to the proximity of phenyl rings.

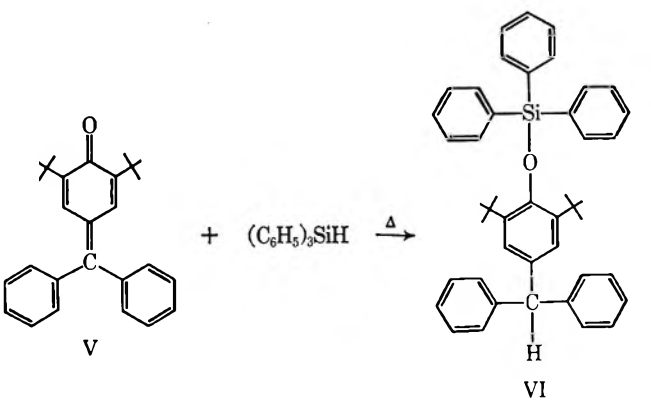
Oxidation of the sterically hindered phenols IIIa–c with active manganese dioxide[3] in benzene solution leads in quantitative yield to deep blue or purple phenoxy radicals IV which were isolated by freeze-



IIIa–c → IVa–c

drying technique. The electron spin resonance (esr) spectra of IVa–c (in benzene) show an unresolved triplet having a peak to peak line width of about 5 G.

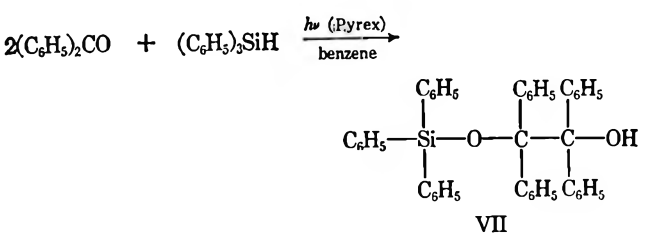
Thermal addition of phenylsilanes was also found to be applicable to other compounds with quinoid structure. Thus, the reaction of triphenylsilane with the quinone methide 3,5-di-*t*-butylfuchsone (V), at 330° results in a 1,6 addition, giving the triphenylsilyl ether of 3,5-di-*t*-butyl-4-hydroxytriphenylmethane (VI).



V + $(C_6H_5)_3SiH$ → VI

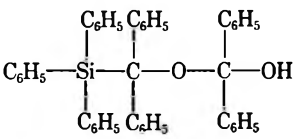
Ultraviolet (uv) irradiation of triphenylsilane in acetone solution reportedly yields the triphenylsilyl ether of isopropyl alcohol.[4] The photochemical reaction of benzophenone with triphenylsilane, however, has not previously been investigated. (The statement[5] that benzophenone does not react photochemically with triphenylsilane seems to be due to an error in translation.) We find that irradiation of a solution of benzophenone and triphenylsilane in benzene, using uv light filtered through Pyrex, results in the rapid formation of the monotriphenylsilyl ether of benzopinacol (VII), isolated in 56% yield. The structure

(1) H. Gilman and D. Wittenberg, *J. Org. Chem.*, **23**, 501 (1958).
(2) A. S. Hay, *Tetrahedron Lett.*, No. 47, 4241 (1965).
(3) *Cf.* H.-D. Becker, *J. Org. Chem.*, **29**, 3068 (1964). Oxidation of 2,4,6-tri-*t*-butylphenol with active manganese dioxide in the presence of other phenols is known to lead to quinol ethers. An attempt to prepare a quinol ether by oxidation of IIIa with active manganese dioxide in the presence of 4-hydroxydiphenylthio ether, however, resulted in the formation of 3,3′,5,5′,-tetra-*t*-butyldiphenoquinone, conceivably involving the hydrolysis of an intermediate quinone ketal.
(4) R. Calas and N. Duffaut, *C. R. Acad. Sci., Paris*, **245**, 906 (1957).
(5) C. Eaborn, "Organosilicon Compounds," Butterworth and Co. Ltd., London, 1960, p 213.



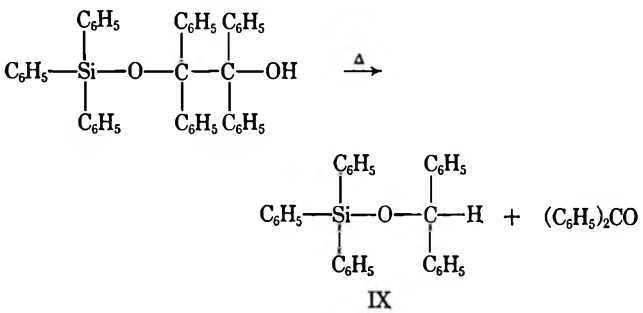
VII

of VII is based on analytical, infrared (ir), and nmr spectroscopic data. The possible isomeric structure VIII is excluded on the basis of the stability of the 2:1



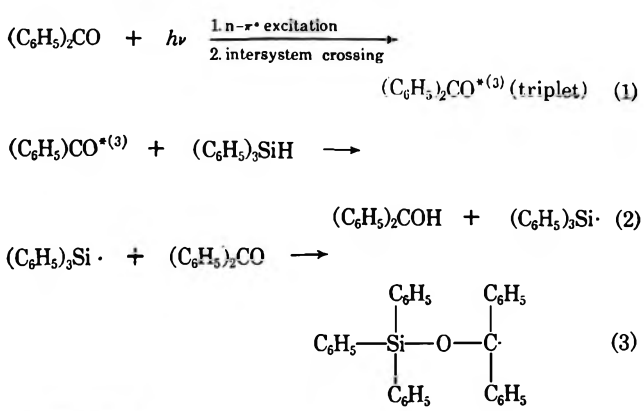
VIII

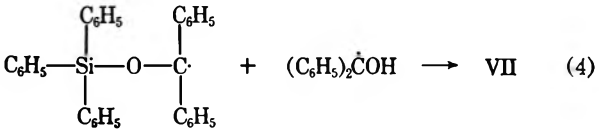
addition product of benzophenone to triphenylsilane toward 2,4-dinitrophenylhydrazine in acidified (H_2SO_4) ethanol.[6] Analogous to the behavior of benzopinacol, upon heating to its melting point, VII smoothly decomposes into the triphenylsilyl ether of benzhydrol IX and benzophenone.[7]



IX

The mechanism of the photochemical formation of VII conceivably involves hydrogen abstraction from triphenylsilane by triplet-state benzophenone to give a ketyl radical and a triphenylsilyl radical (eq 1 and 2). Addition of the silyl radical to ground-state benzophenone and coupling of the ketyl radical with the thus formed carbon radical then leads to the monotriphenylsilyl ether of benzopinacol (eq 3 and 4). It





is worth noting that the 2:1 addition product was also formed as the sole product when benzophenone was used in deficiency.

Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus and are not corrected.

Molecular weights were determined by thermoelectric measurement in benzene.

Addition of Diphenylsilane to 3,3′,5,5′-Tetra-*t*-butyldiphenoquinone (IIIa).—A suspension of tetra-*t*-butyldiphenoquinone (3.05 g, 7.5 mmol) in diphenylsilane (20 ml) was heated under nitrogen to 270–275° whereupon a colorless solution was formed. Diphenylsilane was then removed by vacuum distillation [bp 75° (1 mm)]. The remaining colorless residue was distilled at 1-mm pressure (bp 250–255°) giving 3.54 g (80%) of the monodiphenylsilyl ether of 4,4′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl as a colorless liquid which formed a glass at room temperature.

Anal. Calcd for $C_{40}H_{52}O_2Si$ (592.95): C, 81.03; H, 8.84. Found (565): C, 80.91; H, 9.02.

Addition of Triphenylsilane to 3,3′,5,5′-Tetra-*t*-butyldiphenoquinone (IIIb).—Tetra-*t*-butyldiphenoquinone (2.04 g, 5 mmol) was added to triphenylsilane (5 g) at 250° and the solution was heated for 15 min under nitrogen at 300–310°. Excess triphenylsilane was then removed by vacuum distillation at 1-mm pressure and a bath temperature of 220°. The glassy residue was subjected to vacuum sublimation under the same conditions, giving 2.3 g (69%) of monotriphenylsilyl ether of 4,4′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl as a partly colorless, crystalline (mp ~90°), partly light yellowish glassy sublimate.

Anal. Calcd for $C_{46}H_{56}O_2Si$ (669.05): C, 82.58; H, 8.44. Found (641): C, 82.46; H, 8.33.

Addition of Tribenzylsilane to 3,3′,5,5′-Tetra-*t*-butyldiphenoquinone (IIIc).—A mixture of tetra-*t*-butyldiphenoquinone (2.04 g, 5 mmol) and tribenzylsilane (5.5 g) was heated to 295–300° under nitrogen for 15 min until the dark solution had turned light yellow. The reaction mixture was then subjected to vacuum distillation at 1-mm pressure and a bath temperature of 230–240° to remove excess tribenzylsilane (3.8 g). The glassy residue was triturated with 10 ml of petroleum ether (bp 30–60°) and kept refrigerated overnight, yielding 1.06 g (30%) of the monotribenzylsilyl ether of 4,4′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl as colorless crystals, mp 165–170°.

Anal. Calcd for $C_{49}H_{62}O_2Si$ (711.13): C, 82.76; H, 8.79. Found (707): C, 82.77; H, 8.68.

Oxidation of IIIb with Active Manganese Dioxide to Give IVb.—Active manganese dioxide (10 g) was added under nitrogen to a solution of IIIb (1.0 g) in benzene (100 ml) placed in a screw-cap bottle. The suspension was shaken for 15 min and then filtered through a sintered-glass funnel. The manganese dioxide was washed with 25 ml of benzene and the deep blue filtrate was subjected to freeze drying. The dark blue solid residue (960 mg, 96%) melted between 100 and 110°.

Anal. Calcd for $C_{46}H_{55}O_2Si$ (668.04); C, 82.71; H, 8.30. Found: C, 82.68; H, 8.39.

Oxidation of IIIa to give IVa was carried out in the same manner as that described above. Radical IVa formed a deep purple solid melting ~80° under decomposition.

Anal. Calcd for $C_{40}H_{51}O_2Si$ (591.94): C, 81.16; H, 8.68. Found: C, 80.82; H, 8.56.

Oxidation of IIIc to give IVc was carried out in the same manner as described above for IIIb. Radical IVc formed a deep blue-green solid, melting between 65 and 70°.

Anal. Calcd for $C_{49}H_{61}O_2Si$ (710.12): C, 82.88; H, 8.66. Found: C, 82.50; H, 8.04.

Addition of Triphenylsilane to 3,5-Di-*t*-butylfuchsone (VI).—A mixture of 3,5-di-*t*-butylfuchsone (1.11 g, 3 mmol) and triphenylsilane (2 g, 7.7 mmol) was heated under nitrogen at 330–340° for 5 min. The almost colorless reaction mixture was dissolved in about 5 ml of ether and then diluted with 15 ml of

(6) The 2,4-dinitrophenylhydrazine solution was prepared according to "The Systematic Identification of Organic Compounds," by R. L. Shriner, R. C. Fuson, and D. Y. Curtin, Fourth ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 219.

(7) *Cf.* A. G. Brook, *J. Amer. Chem. Soc.*, **80**, 1886 (1958).

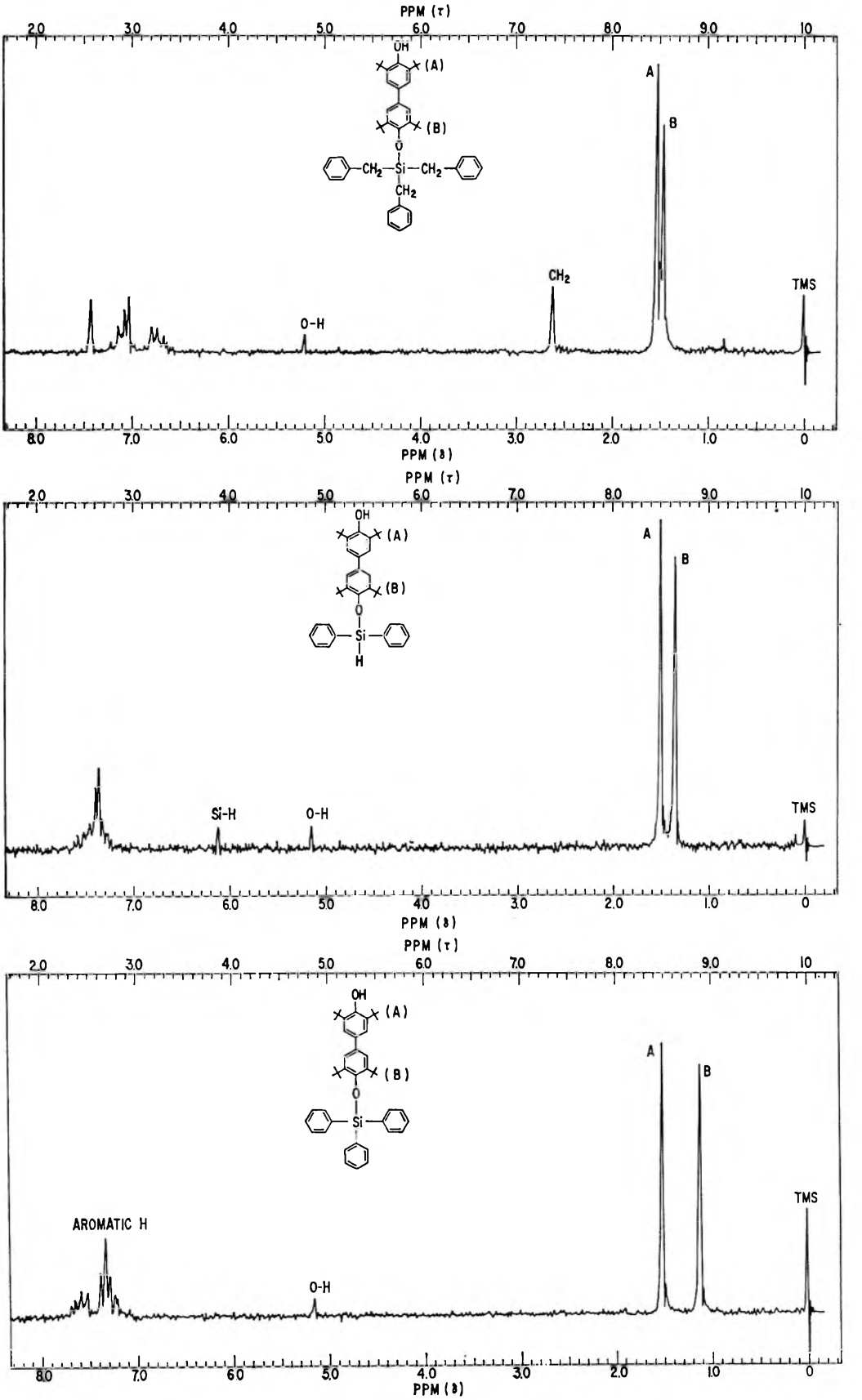


Figure 1.

methanol. After 3 hr, a colorless crystalline precipitate was removed by filtration, dissolved in 5 ml of ether, and filtered to remove traces of insoluble material. The ether filtrate was diluted with 50 ml of methanol, yielding colorless crystals, mp 130–131°, yield 850 mg (45%).

Anal. Calcd for $C_{45}H_{46}OSi$ (630.90): C, 85.66; H, 7.35. Found (623): C, 85.58; H, 7.49.

Photochemical Reaction of Benzophenone with Triphenylsilane to Give VII.—A solution of benzophenone (3.64 g, 20 mmol) and triphenylsilane (2.62 g, 10 mmol) in benzene (60 ml) was irradiated under nitrogen at 16° for 3.5 hr, using a water-cooled immersion well and a 100-W GE mercury lamp, type H 100 A4/T. The solvent was then evaporated *in vacuo* and the sticky, very light yellowish residue was dissolved in 50 ml of ether. The

ether solution was kept standing for 3 hr. The colorless crystalline precipitate formed during that period was removed by filtration: yield 3.5 g (56%), mp 129–131°. The substance can be recrystallized by dissolving it in little chloroform and adding methanol, thus raising the melting point to 132–133° dec.

Anal. Calcd for $C_{44}H_{36}O_2Si$ (624.87): C, 84.58; H, 5.81. Found (637): C, 84.57; H, 6.00.

Thermal Decomposition of VII.—The monotriphenylsilyl ether of benzopinacol (VII, 625 mg, 1 mmol) placed in a sublimator was heated for 15 hr at 95° *in vacuo* (10 mm). The crystalline sublimate was identified as benzophenone (mp 44–45°; mixture melting point with authentic material showed no depression): yield 180 mg (98%). The infrared (ir) spectrum of the glassy residue (molten between plates) was identical with that of the authentic thermal addition product of benzophenone and triphenylsilane.

Spectra.—Ir spectra were obtained with a Perkin-Elmer grating infrared spectrophotometer, Model 521. Nmr spectra were taken on a Varian A-60 spectrometer.

Registry No.—IIIa, 19886-70-5; IIIb, 19886-71-6; IIIc, 19886-72-7; IVa, 19886-73-8; IVb, 19886-74-9; IVc, 19886-75-0; VI, 19886-76-1; VII, 18862-02-7.

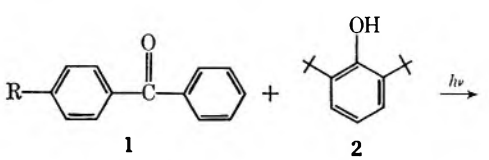
On the Photosensitized Reduction and Addition Reactions of Quinoid Compounds[1]

HANS-DIETER BECKER

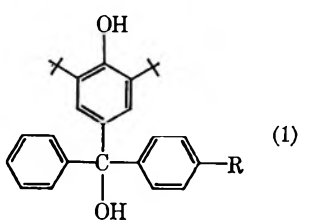
General Electric Research and Development Center, Schenectady, New York 12301

Received October 3, 1968

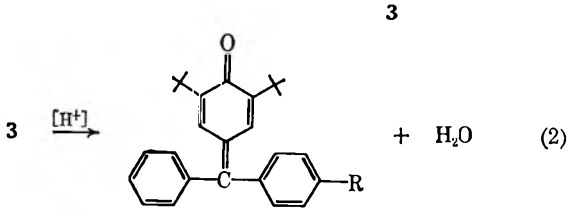
Recently we described the photochemical reaction of benzophenone **1** (R = H) with 2,6-di-*t*-butylphenol **2** leading to bisphenol **5** (R = H) *via* intermediates **3** and **4** according to reactions 1–3.[2] It was suggested that a triplet energy transfer from photoexcited benzophenone to quinone methide **4** was involved in the addition reaction 3 of phenol **2**.



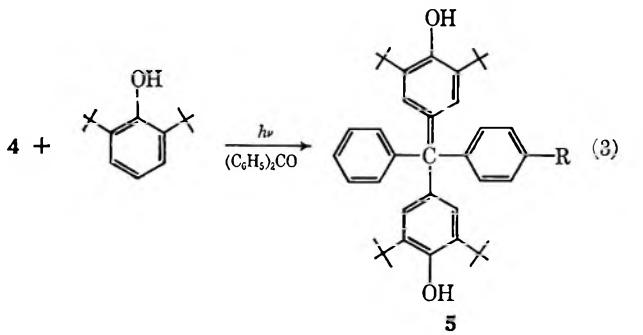
1 **2**



3 (1)

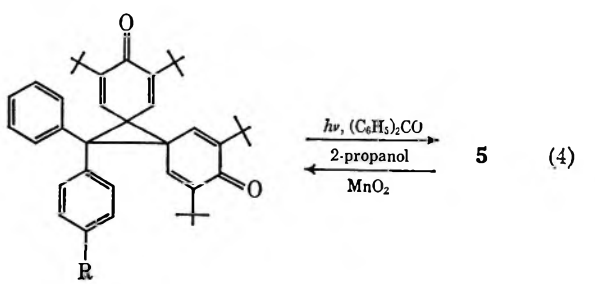


4 (2)

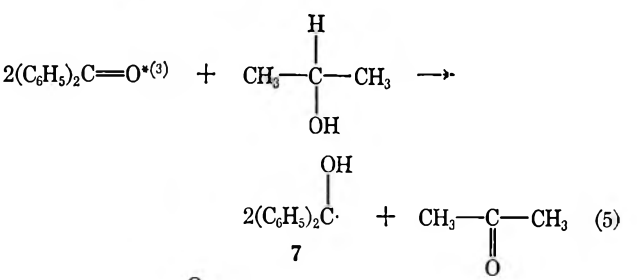


5 (3)

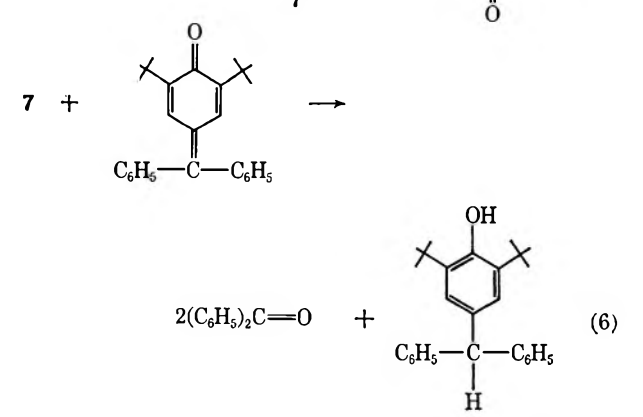
Support for the energy-transfer reaction was deduced from the observation that irradiation of benzophenone in 2-propanol solution containing quinone methide **4** (R = H) did not lead to benzpinacol but resulted in the smooth reduction of the quinone methide. Acetophenone was found to sensitize the reduction in the same manner. During a subsequent investigation[3] we also observed the benzophenone-sensitized reduction of bispirodienone **6** (R = H) in 2-propanol solution to give bisphenol **5** (R = H) (eq 4). Although these reductions appeared well explained by an energy-transfer reaction from benzophenone, the involvement of ketyl radicals **7** as outlined for the benzophenone-sensitized formation of 3,5-di-*t*-butyl-4-hydroxytriphenylmethane **8** was considered in a possible alternative mechanism[4] (eq 5 and 6).



6 **5** (4)



(5)



8 (6)

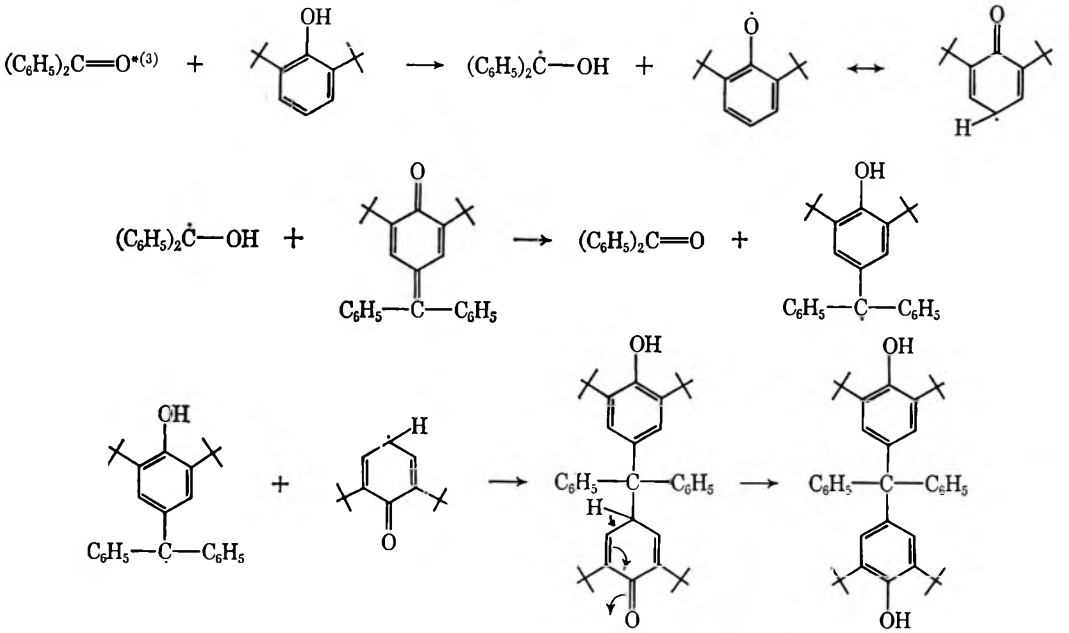
(1) Photochemical Reactions with Phenols. VI. For part V, see H.-D. Becker, *J. Org. Chem.*, **32**, 2140 (1967).

(2) H.-D. Becker, *ibid.*, **32**, 2115 (1967).

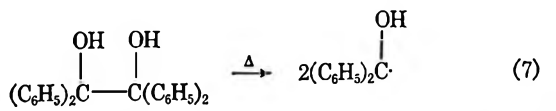
(3) H.-D. Becker, *ibid.*, **32**, 2136 (1967).

(4) A similar mechanism has been proposed earlier for the photochemical reduction of a pyrazolone azomethine dye: W. F. Smith and B. R. Rossiter, *J. Amer. Chem. Soc.*, **89**, 717 (1967).

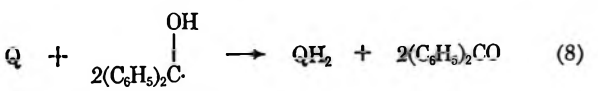
SCHEME I



A recent report[5] on reactions of diphenylhydroxymethyl radicals formed by thermal dissociation of benzpinacol has prompted us to examine the validity of this mode of reduction. We have now found that quinoid compounds Q indeed are easily reduced to QH_2 by diphenylhydroxymethyl radicals generated by this nonphotochemical method (eq 7 and 8). Thus, heating a



(7)



(8)

solution of quinone methide **4** (R = H) (1 mmol) in the presence of an equimolar amount of benzpinacol in dimethylformamide to 160° for 3 min smoothly leads to 3,5-di-*t*-butyl-4-hydroxytriphenylmethane which was isolated in 92% yield. Bispirodienone **6** (R = H) was reduced in the same manner giving bisphenol **5** (R = H) in 97% yield. Likewise, heating a solution of 3,3′,5,5′-tetra-*t*-butyldiphenoquinone in the presence of an equimolar amount of benzpinacol results in the smooth formation of 4,4′-dihydroxy-3,3′,5,5′-tetra-*t*-butylbiphenyl (97% yield).

In view of these findings, the photosensitized reduction of quinone methide **4** and bispirodienone **6** most likely does not involve the previously[2,3] proposed triplet energy-transfer reaction, but proceeds *via* diphenylhydroxymethyl radicals and dimethylhydroxymethyl radicals. Furthermore, the earlier[2,6] invoked energy-transfer mechanism for the photosensitized addition of phenols to quinone methides now seems doubtful. More likely, the role of benzophenone or acetophenone in the addition reaction (3) also is that of a hydrogen carrier as outlined in Scheme I. The previously described advantageous effect of protons on the addition reaction conceivably consists in the acid catalysis of the tautomerization step.

(5) D. C. Neckers and A. P. Schaap, *J. Org. Chem.*, **32**, 22 (1967).
(6) H.-D. Becker, *ibid.*, **32**, 2131 (1967).

The photosensitized addition to quinone methides has been found to proceed smoothly only with 2,6-disubstituted phenols, suggesting that the lifetime of the corresponding phenoxy radicals may be of importance. Also, the generation of the phenoxy radicals must be a very efficient reaction since these addition reactions do proceed in alcohol solution, including 2-propanol, considered to be an excellent hydrogen donor. It is worth noting, however, that even 4-phenylbenzophenone (**1**, R = phenyl) which is known[7] to abstract hydrogen atoms very inefficiently from 2-propanol reacts smoothly with 2,6-di-*t*-butylphenol as a hydrogen donor. Thus, irradiation of 4-phenylbenzophenone in acetone solution in the presence of 2,6-di-*t*-butylphenol and subsequent acidification gives 3,5-di-*t*-butyl-4′-phenylfuchsone (**4**, R = phenyl) in 63% yield, besides a minor amount of 4-phenylbenzophenonepinacol (7.7% yield). The photochemical reaction of 4-phenylbenzophenone with 2,6-di-*t*-butylphenol in acidified methanol results in the smooth formation of 4,4′-dihydroxy-4″-phenyl-3,3′,5,5′-tetra-*t*-butyltetraphenylmethane (**5**, R = phenyl), which was isolated in 53% yield. 4-Phenylbenzophenonepinacol was isolated in 15% yield. The structure of **5** (R = phenyl) is confirmed by elemental analysis, molecular weight determination, spectroscopic data (ir and nmr), and its oxidative conversion into bispirodienone **6** (R = phenyl).

The photochemical formation of **5** according to reactions 1–3 indicates that dimerization and coupling reactions of diphenylhydroxymethyl radicals are suppressed in the presence of quinoid compounds, apparently because the hydrogen atom transfer reaction as outlined in Scheme I is a highly efficient competing process.

Experimental Section

The photochemical reactions were carried out in a previously described immersion well apparatus.[2] Melting points were taken on a hot-stage microscope. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(7) A. Beckett and G. Porter, *Trans. Faraday Soc.*, **59**, 2051 (1963).

Molecular weights were determined by thermoelectric measurement.

Reduction of Bispirodienone 6 (Standard Procedure).—A solution of bispirodienone 6 (R = H)[2] (575 mg, 1 mmol) and benzpinacol (400 mg, 1.09 mmol) in dimethylformamide (6 ml) was kept at 160° for 3 min. Addition of water to the colorless solution gave a crystalline precipitate of bisphenol 5 (R = H): yield 560 mg (97%); mp 233–234°. The mixture melting point with authentic[2] material was not depressed.

3,5-Di-*t*-butyl-4′-phenylfuchsone (4, R = Phenyl).—A solution of 4-phenylbenzophenone (1, R = phenyl) (1.29 g, 5 mmol) and 2,6-di-*t*-butylphenol (2.06 g, 10 mmol) in acetone (60 ml) was irradiated (GE 100-W AH/4) under nitrogen for 4 hr. Vacuum evaporation of solvent from the light yellow reaction mixture gave an oily residue from which 100 mg (7.7%) of 4-phenylbenzophenonepinacol, mp 193–195°, was removed by filtration after treatment with 10 ml of methanol. Upon acidification of the methanol filtrate with 1 drop of concentrated hydrochloric acid dissolved in 1 ml of methanol, the yellow-orange 3,5-di-*t*-butyl-4′-phenylfuchsone precipitated. It was removed by filtration and recrystallized from a boiling chloroform–methanol mixture: yield 1.42 g (63%); mp 192–193°; uv spectrum (in CH_3OH) λ_{max} 283 mμ (ε 19,000), 387 (31,500).

Anal. Calcd for $C_{33}H_{34}O$: C, 88.74; H, 7.67; mol wt, 446.64. Found: C, 88.80; H, 7.77; mol wt (in benzene), 438.

4,4′-Dihydroxy-4″-phenyl-3,3′,5,5′-tetra-*t*-butyltetraphenylmethane (5, R = Phenyl).—A suspension of 4-phenylbenzophenone (1.29 g, 5 mmol) in a solution of 2,6-di-*t*-butylphenol (1.54 g, 7.5 mmol) in methanol (65 ml) containing hydrochloric acid (0.1 ml) was irradiated under nitrogen for 3 hr (Philips HPK, 125 W). A colorless precipitate formed as the benzophenone dissolved during the reaction. Partial vacuum evaporation of the solvent gave 1.7 g of crystalline residue. It was treated with 200 ml of boiling methanol. Hot filtration gave 200 mg (15%) of methanol-insoluble 4-phenylbenzophenonepinacol, mp 198–199° (lit.[8] mp 198–199°).

Anal. Calcd for $C_{38}H_{30}O_2$: C, 88.00; H, 5.83; mol wt, 518.62. Found: C, 87.85; H, 5.82.

After partial vacuum evaporation of the solvent from the filtrate crystalline bisphenol 5 (R = phenyl) precipitated: yield 1.3 g (53%); mp 169–170°.

Anal. Calcd for $C_{47}H_{56}O_2$: C, 86.45; H, 8.65; mol wt, 652.92. Found: C, 86.31; H, 8.82; mol wt (in acetone), 610.

Oxidation of 4,4′-Dihydroxy-4″-phenyl-3,3′,5,5′-tetra-*t*-butyltetraphenylmethane (6, R = Phenyl).—A suspension of active manganese dioxide[9] (6.5 g) in a solution of 5 (R = phenyl) (652 mg, 1 mmol) in benzene (50 ml) was shaken for 30 min. Filtration and vacuum evaporation of the filtrate gave a solid orange residue which was recrystallized by dissolving it in a little warm benzene and adding methanol: yield 600 mg (92%); mp 240–250° dec; ir spectrum (in KBr), no OH absorption, cyclohexadienone absorption at 1620–1645 cm^{-1}.

Anal. Calcd for $C_{47}H_{54}O_2$: C, 86.72; H, 8.36; mol wt, 650.90. Found: C, 86.56; H, 8.36; mol wt (in benzene), 639.

Registry No.—4 (R = Ph), 19886-68-1; 5 (R = Ph), 19886-69-2; 6 (R = Ph), 19922-48-6.

(8) M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.*, **49**, 236 (1927).

(9) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. N. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

The Action of Triethyl Phosphite on 1,5-Diphenyl-3-methyl-4-nitrosopyrazole. A Novel Cleavage of the Pyrazole Ring

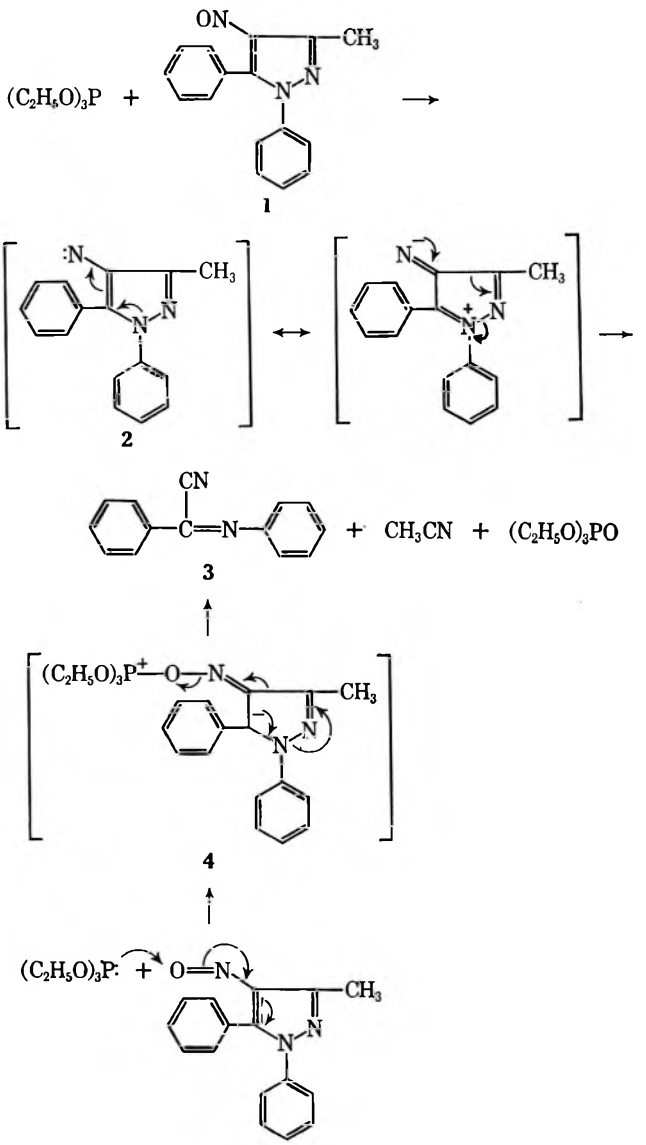
JOHN B. WRIGHT

The Upjohn Company, Research Division, Kalamazoo, Michigan

Received December 31, 1968

Bunyan and Cadogan[1,2] have shown that 2-nitrosodiphenyl reacts with triethyl phosphite at 0–5° in benzene solution to give carbazole in 78% yield. It was postulated that an intermediate nitrene may be involved.[2,3] We were interested in investigating the readily available 1,5-diphenyl-3-methyl-4-nitrosopyrazole[4] (1) in this reaction. The nitrene intermediate from 1 might lead to an indolo[2,3-*d*]pyrazole, but alternatively, the singlet nitrene might be expected also to attract electrons from the pyrazole ring.

SCHEME I



When 1,5-diphenyl-3-methyl-4-nitrosopyrazole (1) was treated with triethyl phosphite in benzene solution at 0–5°, according to the general method of Bunyan and Cadogan,[2] no apparent reaction took place. However, when the mixture was heated under reflux, a yellow solid, $C_{14}H_{10}N_2$, was isolated. The ir spectrum

(1) P. J. Bunyan and J. I. G. Cadogan, *Proc. Chem. Soc.*, 78 (1962).
(2) P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 42 (1963).
(3) J. I. G. Cadogan, *Quart. Rev.* (London), **22**, 222 (1968).
(4) C. N. O'Callaghan and D. Twomey, *Proc. Roy. Irish Acad. Sect. B.*, **64** (13), 187 (1965); *Chem. Abstr.*, **65**, 12191*d* (1966).

showed weak absorption at 2210 cm^{-1}, attributable to a nitrile group, and no NH or OH absorption. The nmr spectrum showed only aromatic protons and *no* CH_3 protons. These data were consistent with phenyl(phenylimino)acetonitrile (**3**), and this structure was confirmed by comparison (infrared, melting point, and nuclear magnetic resonance) with an authentic sample.[5]

Subsequently, it was found that the reaction could be carried out somewhat more conveniently by simply heating equimolar amounts of 1,5-diphenyl-3-methyl-4-nitrosopyrazole (**1**) and triethyl phosphite on the steam bath. An exothermic reaction took place and a small amount of liquid distilled from the reaction mixture. Redistillation of the distillate gave a colorless liquid boiling at 80° which was identified as acetonitrile. Phenyl(phenylimino)acetonitrile (**3**) was obtained from the reaction mixture in 70% yield.

The products obtained may be explained by the mechanism outlined in Scheme I. The reaction is thus a type of heterolytic fragmentation[6] which differs from those investigated previously in that a nitrene **2** may be involved as an intermediate. However, it is possible that a concerted reaction (*e.g.*, **4**) takes place without the formation of an intermediate nitrene.[7]

Experimental Section[8]

Phenyl(phenylimino)acetonitrile (5).—A mixture of 7.89 g (0.03 mol) of 1,5-diphenyl-3-methyl-4-nitrosopyrazole,[4] 4.98 g (0.03 mol) of triethyl phosphite, and 120 ml of dry benzene was heated under reflux for 13 hr using a condenser closed off with a calcium chloride tube. The benzene was removed by distillation and the residue was heated on the steam bath under vacuum (<1 mm). The oil was allowed to cool and was poured into water. The solid was removed by filtration and was recrystallized from ethanol. There was obtained 3.05 g of yellow prisms melting at 73–74°.

Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.40; H, 4.82; N, 13.70; *m/e*, 206.

When equimolar amounts [7.89 g (0.03 mol) of 1,5-diphenyl-3-methyl-4-nitrosopyrazole and 4.98 g (0.03 mol) of triethyl phosphite] of reactants were heated on the steam bath without any solvent in a flask containing a side arm for distillation, an exothermic reaction took place and several milliliters of distillate was obtained. The residue was poured into water and the solid was removed by filtration and recrystallized from ethanol. There was obtained 4.34 g (70%) of yellow-green platelets melting at 67–71°. Further recrystallization from ethanol raised the melting point to 73–74°. The product was identical (mixture melting point and comparison infrared spectra) with that obtained above.

Registry No.—**1**, 7171-64-4; **3**, 4686-14-0; triethyl phosphite, 122-52-1.

Acknowledgment.—The author is indebted to Professors Donald J. Cram, Kenneth Rinehart, and William Doering for stimulating discussions and to Mr. Albert Lallinger for technical assistance.

(5) F. Kröhnke, *Ber.*, **71B**, 2583 (1938). The reported melting point is 72°.

(6) *Cf.* C. A. Grob and P. W. Schiess, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1 (1967).

(7) W. D. Crow and C. Wentrup [*Chem. Commun.*, 1082 (1968)] have recently investigated heterocyclic nitrenes in the pyridine and pyrimidine series and found that in these cases ring contraction takes place. The nitrenes were prepared by pyrolysis of triazolo[4,5-*b*]pyridine, tetraazolo-[1,5-*a*]pyrimidines, and related substances.

(8) All melting points and boiling points are corrected.

Formation of Thiols from Thiophene and Benzyne at 690°

ELLIS K. FIELDS

Research and Development Department, Amoco Chemicals Corporation, Whiting, Indiana

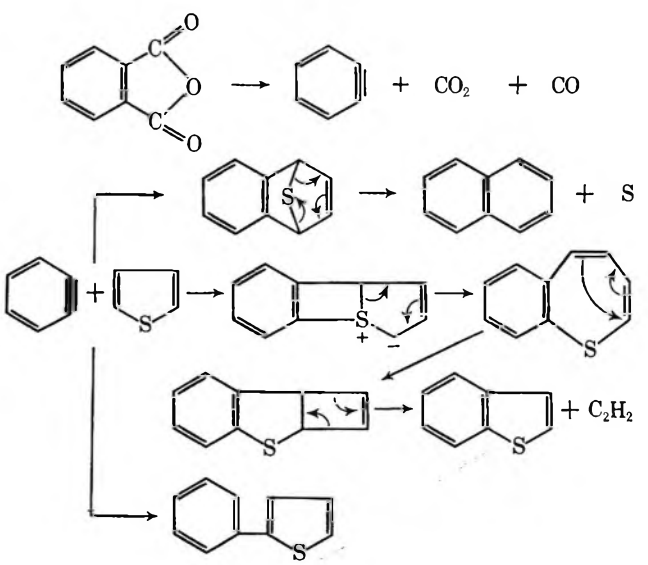
AND SEYMOUR MEYERSON

Research and Development Department, American Oil Company, Whiting, Indiana

Received November 18, 1968

Benzyne from phthalic anhydride reacts with thiophene at 690° to give naphthalene and benzothiophene by 1,4 and 1,2 addition, respectively, as well as phenylthiophene by insertion (Scheme I).[1] The ratio of naphthalene to benzothiophene is about 9:1, implying nearly the same preference for 1,4 over 1,2 addition as was inferred from the reaction of benzyne with dichlorobenzenes and pyridine at the same temperature,[2,3] and reflecting the strong tendency of benzyne to act as a dienophile at high temperatures as well as in solution.[4]

SCHEME I



As the formation of naphthalene from phthalic anhydride and thiophene requires the extrusion of a sulfur atom, products arising from the reaction of such sulfur, possibly monatomic and hence highly reactive,[5] with thiophene might be expected. Sulfur atoms have been formed by photolysis of COS rather than by heating sulfur; the high S–S bond energy of about 101 kcal/mol[6] would ordinarily require temperatures at which

(1) (a) E. K. Fields and S. Meyerson, *Chem. Commun.*, 708 (1966); (b) E. K. Fields and S. Meyerson in "Organosulfur Chemistry," M. J. Janssen, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 143.

(2) S. Meyerson and E. K. Fields, *Chem. Ind.* (London), 1230 (1966).

(3) E. K. Fields and S. Meyerson, *J. Org. Chem.*, **31**, 3307 (1966).

(4) G. Wittig, *Angew. Chem.*, **69**, 245 (1957); T. G. Corbett and O. N. Porter, *Aust. J. Chem.*, **18**, 781 (1965); W. L. Dilling, *Tetrahedron Lett.*, 939 (1966).

(5) K. S. Sidhu, E. M. Lown, O. P. Strausz, and H. E. Gunning, *J. Amer. Chem. Soc.*, **88**, 254 (1966).

(6) R. F. Palmer and F. P. Lossing, *ibid.*, **84**, 4661 (1962); J. Berkowitz and J. R. Marquart, *J. Chem. Phys.*, **39**, 275 (1963); H. Mackle, Abstracts of the Sulfur Symposium, Calgary, March 1964.

most reaction products decompose.[7] Indeed, the mass spectrum of the products revealed a substance of molecular weight 116 and an isotopic distribution establishing the elemental composition as $C_4H_4S_2$, apparently thiophenethiol. The relative amounts of the major products are shown in Table I. The product mixture

TABLE I

Product	Rel concn[a]
Thiophenethiol	9.2
Naphthalene	100.0
Benzothiophene	11.3
Phenylthiophene	83.4
Bithiophene	62.6

[a] Relative intensity in the low-voltage (7.5 V, uncorrected) mass spectrum, normalized to naphthalene = 100.

was extracted with potassium hydroxide and the recovered alkali-soluble products were analyzed by directly coupled gas chromatography–mass spectrometry[8] and compared with an authentic sample of thiophene-2-thiol. The latter was synthesized from 2-thienylmagnesium bromide and sulfur;[9] its mass spectrum showed it to consist essentially of two components, thiophenethiol, presumably the 2 isomer, and dithienyl sulfide, presumably the 2,2′ isomer. An attempt was made to purify the material by gas chromatography. The mass spectrum of the supposedly purified thiol showed again the same two components, but, unexpectedly, enriched in the sulfide. The relative concentrations in the two samples differed sufficiently to permit use of the procedure described by Meyerson[10] to derive reference spectra for the components and to analyze the two mixtures quantitatively. The concentrations (volume per cent) of thiophenethiol and dithienyl sulfide, respectively, were, in the original sample, 92.4 and 7.6 and, in the chromatographed sample, 63.0 and 37.0.

In deriving the spectra of these two compounds we ignored the possible presence of any other components; we assumed that the peak at 198 was due solely to the dithienyl sulfide, and that the peak at 116, after removal of heavy-isotopic contributions, was due solely to the thiophenethiol. The fact that the derived spectra contain very few and very small negative values supports the validity of these assumptions.

The unexpected enrichment of the gas-chromatographic trapout in the sulfide suggests that it was formed by a reaction on the column and, further, that it had a retention time identical with that of the thiophenethiol. Gas chromatography was run on a 6 ft × 0.25 in. diameter column containing diethylene glycol sebacate on 30–60 mesh Chromosorb W. Other thiols, *n*-octyl- and *n*-decylthiol, thiophenol, and thio-*o*-cresol, did not show the same behavior; they were unchanged after several passages through the column.

The separated product from the reaction of phthalic anhydride with thiophene, with the parent peak at mass 116, again accompanied by heavy-isotopic satellites with an intensity distribution indicating the formula $C_4H_4S_2$, gave a spectrum qualitatively similar to that of thiophene-2-thiol in the API Catalog[11] and to that of our synthesized sample. Partial spectra, consisting of most prominent peaks, are shown in Table II. The derived spectrum of the synthesized thiophenethiol is in good agreement with the published spectrum, but differs appreciably from that of the benzyne reaction product. The differences, in the light of correlations described by Foster, *et al.*,[12] suggest that the material from the benzyne reaction consists largely of the 3 isomer. The substantially lower relative intensity at the parent mass parallels the known lower stability of this isomer to light, heat, and air.[9]

TABLE II

Mass	Product of mol wt 116	API Spectrum No. 162[11]	Synthesized thiophene-2-thiol[a]
45	69.6	45.5	33.0
71	100.0	93.4	89.6
115	7.22	9.25	8.66
116	45.4	100.0	100.0

[a] Spectrum derived from those of thiol–sulfide mixtures.[10]

Thiophenethiol, about 10% as much as bithiophene, was also found in the product when a solution of sulfur in thiophene was pyrolyzed under the identical conditions as for phthalic anhydride and thiophene.

Major alkali-soluble products from the reaction of phthalic anhydride with thiophene and of thiophene with sulfur, both at 690°, are shown in Table III. Relative concentrations are approximated by relative intensities in the low-voltage mass spectra. Sensitivity, *i.e.*, the proportionality factor between parent peak intensity and concentration, differs from one compound to another; however, closely related compounds have roughly equal sensitivities at the ionizing voltage employed in our work.[13] For example, from the reaction of phthalic anhydride with thiophene, relative intensities of the four products listed in Table IV, normalized to a total of 100.0, agree quite well with relative areas in the gas chromatogram.

TABLE III

ALKALI-SOLUBLE PRODUCTS FROM PHTHALIC ANHYDRIDE WITH THIOPHENE AND THIOPHENE WITH SULFUR[a]

Mass	Probable structure	Rel concn[b] of product Expt A[c]	Expt B[d]
116	Thiophenethiol	100	100
160	Naphthalenethiol	78	
198	Bithiophenethiol	4	3
230	Bithiophenedithiol	1	147

[a] Conditions: 690°, 12-sec contact time. [b] Relative intensities in the low-voltage (7.5 V, uncorrected) mass spectrum. [c] Phthalic anhydride (0.2 mol) and thiophene (2.0 mol). The products weighed 3.2 g. [d] Sulfur (0.2 g-atom) and thiophene (0.4 mol). The products weighed 1.35 g.

The thiol of mol wt 230 listed as bithiophenedithiol in Table III, but which may also contain isomeric dithienyl sulfide thiols, was present in larger concentration than any other component. However, there seems no obvious reason why such large amounts of these com-

(7) H. E. Gunning and O. P. Strausz, *Advan. Photochem.*, **4**, 141 (1966).

(8) R. S. Gohlke, *Anal. Chem.*, **31**, 535 (1959); L. P. Lindeman and J. L. Annis, *ibid.*, **32**, 1742 (1960); J. T. Watson and K. Biemann, *ibid.*, **36**, 1135 (1964).

(9) N. H. Houff and R. D. Schultz, *J. Amer. Chem. Soc.*, **75**, 6316 (1953).

(10) S. Meyerson, *Anal. Chem.*, **31**, 174 (1959).

(11) American Petroleum Institute, Research Project 44, "Catalog of Mass Spectral Data," Chemical Thermodynamics Properties Center, Agricultural and Mechanical College of Texas, College Station, Texas, 1947–1967.

(12) N. G. Foster, D. E. Hirsch, R. F. Kendall, and B. H. Eccleston, U. S. Department of the Interior, Bureau of Mines, Report of Investigations, No. 6433, 1963.

(13) G. F. Crable, G. L. Kearns, and M. S. Norris, *Anal. Chem.*, **32**, 13 (1960).

TABLE IV

Component	Rel intensity in mass spectrum	Rel area in gas chromatogram
Naphthalene	38.9	47.8
Benzothiophene	4.4	5.1
Phenylthiophenes	32.4	27.7[a]
Bithienyls	24.3	19.4

[a] 2-Phenyl, 20.9; 3-phenyl, 6.8.

To confirm the origin of the product from phthalic anhydride with thiophene, we ran the same reaction using phthalic anhydride-d_4. The major products are shown in Table VI, together with those from the unlabeled anhydride for comparison.

We had hoped to find naphthalenethiol-d_4 from the labeled phthalic anhydride reaction; if present, however, it was obscured by phenylthiophene-d_4 of the same

TABLE V

ISOTOPIC PROFILES OF THIOLS

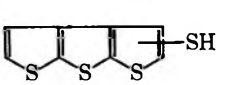
Thiol	Formula	Mass	Rel intensity[a] Measd: Phthalic anhydride with thiophene	Rel intensity[a] Measd: Sulfur with thiophene	Rel intensity[a] Calcd
Thiophenethiol	$C_4H_4S_2$	116	100	100	100
		117	6.97	6.81	5.99
		118	9.03	9.14	8.99
		119	0.47	0.49	0.45
		120			0.23
Naphthalenethiol	$C_{10}H_8S$	160	100	0	100
		161	12.5		11.7
		162	5.6		5.06
		163	0.9		0.49
		164			0.04
Bithiophenethiol	$C_8H_6S_3$	198	100	100	100
		199	13	14.7	11.1
		200	13	13.3	13.8
		201			1.37
		202			0.69
Bithiophenedithiol	$C_8H_6S_4$	230	100	100	100
		231	33[b]	12.4	11.9
		232	33[b]	18.1	18.3
		233		2.1	2.0
		234		1.4	1.3

[a] 7.5-V spectrum. [b] Quite different from the calculated values, most likely due to the very low signal-to-noise ratio.

pounds should be formed, whatever their structure. Further work to answer this question is in progress.

At the mole ratio of phthalic anhydride/thiophene of 1:5, the relative amount of thiols changed appreciably. Determined by gas chromatography, these follow, volume per cent: thiophene-3-thiol, 2.3; thiophene-2-thiol, 12.0; naphthalenethiol, 84.5; unknown thiols, 1.2. The naphthalenethiol may be a mixture of the 1 and 2 isomers; we were unable to separate authentic samples of the two.

Table V compares the measured isotopic profiles of the thiols listed in Table III with calculated profiles. There was additionally some product of mol wt 228 in the alkali-soluble material (7 on the scale of Table III) from thiophene and sulfur, possibly thienothiophthenethiol. However, its isotopic profile overlapped



that of the thiol of mol wt 230 and could not be determined. The agreement between measured and calculated isotopic profiles is generally good, and together with the solubility in alkali indicates the nature of the thiols formed in the two reactions. This method of analysis does not, of course, differentiate among possible structural isomers. Such an analysis would be extremely difficult, even assuming no fortuitous coincidences of retention times among isomers of their impurities, as we have described for 2-thiophenethiol and the corresponding sulfide.

TABLE VI

PRODUCTS FROM THIOPHENE WITH PHTHALIC ANHYDRIDE-d_0 AND -d_4[a]

Product	Rel concn[b] Phthalic-d_0	Rel concn[b] Anhydride-d_4[c]
Thiophenethiol	2	2
Naphthalene	26	
Naphthalene-d_4		27
Benzothiophene	3	
Benzothiophene-d_4		3
Thiophthene	0.5	0.9
Phenylthiophene	10	
Phenyl-d_5-thiophene		9
Bithiophene	12	17
Benzothiophthene	12	
Benzothiophthene-d_4		9

[a] Conditions: 690°, 7-sec contact time, mole ratio of phthalic anhydride/thiophene, 10:1. [b] Relative intensities in the low-voltage mass spectrum, normalized to mass 116, thiophenethiol = 2. [c] 94.3% d_4, 5.7% d_3.

molecular weight (164) and formed in much greater amount. Both reactions showed the same preference, 9:1, for benzyne to act as a dienophile and add 1,4 rather than 1,2 to thiophene.

Although the amount of sulfur from the reaction of phthalic anhydride with thiophene could theoretically be no greater than that in the sulfur–thiophene reaction and from the total product analysis[1] was appreciably less, the yield of thiols in the first reaction was far greater than that in the second. This result, coupled with Hartough's findings that sulfur and thiophene failed to

react at 600°,[14] is good evidence for the high reactivity of sulfur lost from the benzyne–thiophene 1,4 adduct I. The formation of thiols in the reactions of other arynes with thiophene and benzothiophene is being investigated; in addition, we are looking at the reactions of other arynes generated by pyrolysis of aromatic anhydrides with sulfur, carbon disulfide, and S-containing heterocyclic compounds other than thiophene.

Experimental Section

Reaction of Phthalic Anhydride with Thiophene.—A filtered solution of 14.8 g (0.1 mol) of phthalic anhydride in 78.65 ml (1 mole) of thiophene was pyrolyzed at 690° in a Vycor tube filled with Vycor chips in a stream of dry nitrogen flowing at 20 cc/min. The pyrolysate was distilled to recover 67.5 ml of thiophene and obtain 12.15 g of residue.

A solution of the residue in 200 ml of ether was extracted with two 50-ml portions of 10% aqueous potassium hydroxide; the acidified aqueous extract was extracted with three 50-ml portions of ether. The dried ether solution, evaporated on the steam bath, gave 1.6 g of a light yellow semisolid mixture of thiols.

Reaction of Sulfur with Thiophene.—A mixture of 3.2 g (0.1 g-atom) of sulfur and 31.46 ml (0.4 mol) of thiophene was refluxed for 18 hr, by which time all of the sulfur was in solution. Although a small amount of hydrogen sulfide evolved during the refluxing, there had been no appreciable reaction; both sulfur and thiophene were recovered unchanged in a separate experiment. The thiophene solution was pyrolyzed and the thiols were worked up as described in the phthalic anhydride reaction. Yield of mixed thiols was 0.25 g.

Phthalic anhydride-d_4 was made by oxidation of naphthalene-d_8 with potassium permanganate.

Analysis.—Mass spectral analyses were performed on a Consolidated Model 21-103c instrument with the inlet system at 250°. The usual 70-V spectrum was supplemented by a low-voltage (7.5 ionizing V, uncorrected) spectrum to help identify parent peaks.

Gas chromatographic analyses were performed on a stainless steel column 6 ft long and 0.25-in. o.d., packed with 10% diethylene glycol sebacate on 30–60 mesh acid-washed Chromosorb W. The column temperature was programmed from 70 to 200° at 2°/min; helium flow was 50 cc/min. Temperature of the injector was 240°; that of the thermal conductivity cell was 300°.

Directly coupled gas chromatography–mass spectrometry is described in ref 8.

Registry No.—Thiophene, 110-02-1; benzyne, 462-80-6.

(14) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p 61.

Synthesis of Isoquinolines. X. 1-Alkyl-1,2,3,4-tetrahydroisoquinolines[1]

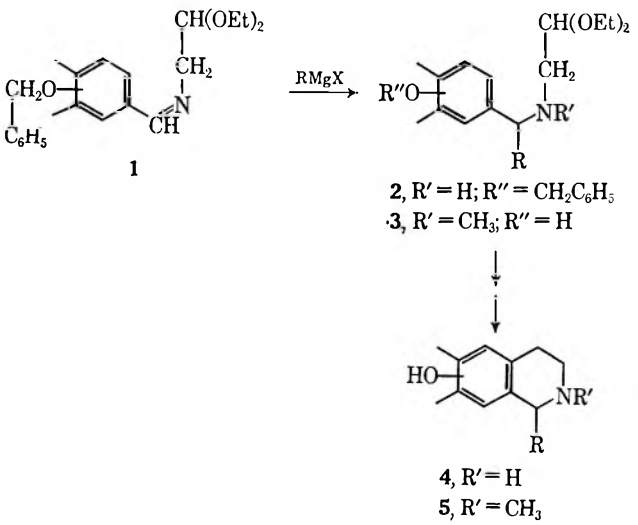
J. M. BOBBITT, A. S. STEINFELD,[2] K. H. WEISGRABER,[2] AND S. DUTTA

Department of Chemistry, The University of Connecticut, Storrs, Connecticut 06268

Received December 30, 1968

In recent years, we have developed some facile syntheses of various oxygenated isoquinolines.[3] In connection with our work on the oxidative coupling of phenolic isoquinolines,[4,5] we required a series of 1-alkyl-N-methyl-1,2,3,4-tetrahydroisoquinolines. In this paper, we would like to describe a general synthesis of these compounds.[6] The reactions are shown in Scheme I.

SCHEME I



This route for the preparation of 1-alkylisoquinolines was originally developed by Quelet and Vinot.[7] However, their method involved the use of boron trifluoride as a cyclizing agent. This was found to be generally unsuitable for the preparation of oxygenated isoquinolines, and thus, for the various cactus alkaloids.[8] Vanillin and isovanillin were benzylated[9] (75–85% yield) and allowed to react with aminoacetaldehyde diethyl acetal to yield the Schiff bases **1** (95% yield). Veratraldehyde was converted directly to the Schiff base. The Schiff bases were allowed to react with various aliphatic Grignard reagents to yield the amines (**2**, R = CH_3, CH_3CH_2, and $CH_3CHCH_3CH_2$). At this point, there were two alternatives. Compounds **2** could be debenzylated (H_2–Pd/C), hydrolyzed, and cyclized (HCl), and reduced to give 1-alkyl-1,2,3,4-tetrahydroisoquinolines (**4**, Table I).[10] Second, compounds **2** could be debenzylated, N-methylated (HCHO, H_2, Pt) to **3**, hydrolyzed, cyclized, and reduced to yield 1-alkyl-N-methyl-1,2,3,4-tetrahydroisoquinolines (**5**, Table II).[11]

Several alkaloids were prepared in this work. These are salsoline (**6**),[8] salsolidine (**8**),[8] carnegine (**13**),[8] and lophocerine (**16**).[12]

(1) (a) Paper IX. M. Bobbitt and C. P. Dutta, *J. Org. Chem.*, **34**, 2001 (1969). (b) This work was sponsored, in part, by Training Grant GM-1139 from the National Institutes of Health.

(2) Abstracted in part from the Ph.D. Dissertations of A. S. S. (University of Connecticut, 1968) and K. H. W. (University of Connecticut, 1969).

(3) See ref 1 and the preceding papers of this series.

(4) J. M. Bobbitt, R. Ebermann, and M. Schubert, *Tetrahedron Lett.*, 575 (1963).

(5) J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind.* (London), 2127 (1966).

(6) This work was partially reported at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(7) N. Vinot, *Ann. Chim.* (Paris), [13] **3**, 461 (1958); N. Vinot and R. Quelet, *Bull. Soc. Chim. Fr.*, 1164 (1959).

(8) These compounds have been previously synthesized, generally by more laborious routes. The work is summarized by L. Reti in "The Alkaloids," Vol. IV, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1954, p 7.

(9) R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1888 (1927).

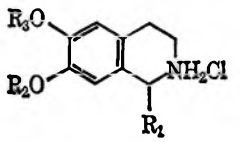
(10) J. M. Bobbitt, J. M. Kiely, K. W. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1963).

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

(12) J. M. Bobbitt and T.-t. Chou, *ibid.*, **24**, 1106 (1959).

TABLE I

1-ALKYL-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES



Compd	R_1	R_2	R_3	Yield,[a] %	Mp, °C	Lit. mp, °C
6	CH_3	CH_3	H	65	200	200–202[b]
7	CH_3	H	CH_3	83	236–237	237–238[c]
8	CH_3	CH_3	CH_3	66	189–191	196–197[d]
9	C_2H_5	CH_3	H	68	190–191	186–188[e]
10[f]	C_2H_5	H	CH_3	81	218–220	

[a] The yields are based upon the starting Schiff bases 1. [b] N. Proskurnina and A. Orekhoff, *Bull. Soc. Chim. Fr.*, [5] **4**, 1265 (1937). The literature contains melting points for this compound ranging from 145 to 220°. [c] H. Bruderer and A. Brossi, *Helv. Chem. Acta*, **48**, 1945 (1965). [d] E. Späth and F. Dengel, *Ber.*, **71**, 113 (1938). [e] D. Beke and C. Szántay, *Magy. Kém. Folyóirat*, **60**, 346 (1954); *Chem. Abstr.*, **52**, 4648 (1958). [f] *Anal.* Calcd: C, 59.09; H, 7.39; N, 5.74. Found: C, 59.06; H, 7.52; N, 5.93.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.45; H, 7.61; N, 3.95.

The base from benzylisovanillin melted at 70–71°.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.23; H, 7.72; N, 4.15.

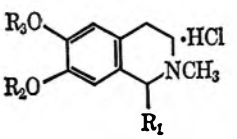
Grignard Synthesis of 2.—Commercial Grignard reagent[16] (0.06 mol) was diluted with 200 ml of dry ether in an anhydrous system. The reaction mixture was cooled to 0° and stirred, and a solution of 0.02 mol of Schiff base 1 in 100 ml of dry ether was added slowly (0.5 hr). The mixture was stirred at reflux temperature until tlc showed the absence of starting material[17] (18–24 hr). The reaction was cooled to 0° and hydrolyzed with NH_4Cl (9 g in 25 ml of H_2O). The mixture was heated to reflux for 1 hr, cooled, and separated. The aqueous layer was extracted twice with ether and the combined ether layer and extracts were washed (H_2O), dried (Na_2SO_4), and evaporated to a thick oil 2 on a rotary evaporator.

The benzyl compounds were debenzylated by dissolving them in 30 ml of ethanol and hydrogenating them over 3.5 g of 5% Pd on C. The catalyst was removed by filtration and the solvent was evaporated on a rotary evaporator to yield oily products.

1-Alkyl-1,2,3,4-tetrahydroisoquinolines (4).—The appropriate benzylamino acetals (from 0.02-mol runs) obtained from debenzylation were dissolved in 50 ml of 4 *N* HCl, extracted twice with ether–benzene, and allowed to stand for 14–18 hr. The

TABLE II

1-ALKYL-N-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES



Compd	R_1	R_2	R_3	Yield,[a] %	Mp, °C	Lit. mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	CH_3	CH_3	H	28	253–255		59.13	7.39	5.74	58.51	7.22	6.07
12	CH_3	H	CH_3	62	195–198	190–192[b]						
13	CH_3	CH_3	CH_3	62	209–210	210–211[c]						
14	C_2H_5	H	CH_3	51	174–178		60.56	7.82	5.43	60.28	7.84	5.49
15	C_2H_5	CH_3	H	30	260		60.56	7.82	5.43	59.95	7.44	5.74
16	$CH_3CHCH_3CH_2$	H	CH_3	45	186–187 (picrate)	191–193[d]						

[a] The yields are based upon the starting Schiff bases 1. [b] J. T. Strukov, *Zh. Obshch. Khim.*, **31**, 2709 (1961); *Chem. Abstr.*, **56**, 11567 (1962). [c] E. Späth, *Ber.*, **62**, 1021 (1929). [d] Reference 12.

Experimental Section[13]

Benzylation of Phenolic Aldehydes.—The aldehyde (0.5 mol) was dissolved in 250 ml of absolute ethanol and added to a mixture of benzyl chloride (83 g, 0.66 mol) and K_2CO_3 (72 g, 0.52 mol) in 200 ml of absolute ethanol. The solution was heated to reflux for 15 hr with stirring. Activated carbon (5 g) and 100 ml more of ethanol were added and the mixture was heated for 0.5 hr more and filtered hot. The products precipitated when the filtrate was cooled and were collected by filtration. Benzylvanillin melted at 61–62°, lit.[9] 64–65°, and benzylisovanillin melted at 63–65°, lit.[14] 63°.

The Schiff Bases 1.—The aromatic aldehydes (0.1 mol) were dissolved in 100 ml of benzene, combined with 13.3 g (0.1 mol) of aminoacetaldehyde diethyl acetal, and allowed to stand overnight. The solution was heated to reflux under a Dean–Stark tube for 2 hr or until all of the water had collected. The benzene was removed on a rotary evaporator and the products were crystallized from hexane. The base from veratraldehyde melted at 60–62°, lit.[15] 61–63°.

The base from benzylvanillin melted at 34°.

last traces of the organic solvents were removed on a rotary evaporator, and the acid solutions were hydrogenated over 3.5 g of 5% Pd on C. The catalyst was removed by filtration and the solvent was evaporated on a rotary evaporator (below 50°). The residue was dissolved in 50 ml of absolute ethanol and again evaporated. The process was repeated two or three times until the products crystallized. The products were collected and recrystallized from ethanol.

1-Alkyl-N-methyl-1,2,3,4-tetrahydroisoquinolines (5).—The appropriate benzylamino acetals (from 0.02-mol runs) obtained from debenzylation were dissolved in 30 ml of ethanol, mixed with 1.6 ml of acetic acid and 1.5 g of 37% formaldehyde solution, and hydrogenated over 0.3 g of prereduced platinum oxide. The catalyst was filtered and the solvent was removed on a rotary evaporator to yield oily N-methylbenzylamino acetals. These were cyclized in 4 *N* HCl and reduced as described above for 4.

Registry No.—**10**, 19886-92-1; **11**, 19072-60-7; **14**, 19886-94-3; **15**, 19922-52-2; base from benzylvanillin, 19886-95-4; base from benzylisovanillin, 19922-53-3.

(13) Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Microanalyses were performed by the Baron Consulting Co., Orange, Conn. Tlc was carried out on silica gel GF-254 layers and visualized under uv light at 254 mμ.

(14) A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 817 (1930).

(15) R. Forsyth, C. I. Kelly, and F. L. Pyman, *ibid.*, **127**, 1659 (1925).

(16) Methylmagnesium bromide and ethylmagnesium bromide was from the Arapahoe Chemical Co., Boulder, Colo. Isobutyl Grignard reagent was prepared in ether from isobutyl bromide and Mg.

(17) Small samples were removed and hydrolyzed with a few drops of water. The ether layer was spotted and the chromatograms were developed with benzene–methanol, 20:1.

The Reaction of Carbon Suboxide with Some Ketones. Formation and Structure of Pyrones from Acetylacetone, Benzoylacetone, Ethyl Acetoacetate, and Acetone

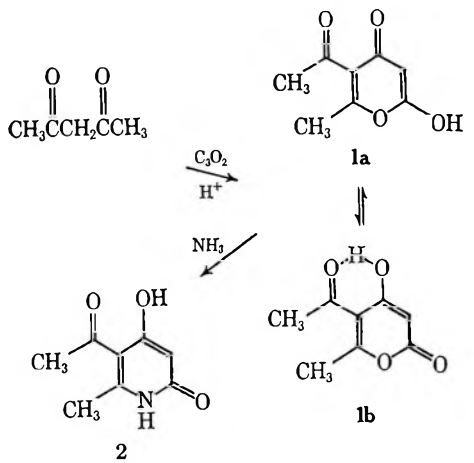
A. OMORI, N. SONODA, AND S. TSUTSUMI

Department of Chemical Technology, Faculty of Engineering, Osaka University, Suita, Osaka, Japan

Received September 3, 1968

The reaction of carbon suboxide and benzaldehyde is reported to give the benzylidene ester of benzalmalonic acid,[1] whereas the reaction of carbon suboxide with some ketones produces pyronopyrone derivatives.[2,3] We now report on the reaction of carbon suboxide with several enolizable ketones.

The reaction of acetylacetone with C_3O_2 at 0–5° in the presence of sulfuric acid gave the 1:1 adduct, pyrone **1**, in 85% yield. The pyrone structure was



based on spectral data and conversion of **1** into the corresponding pyridone (**2**).[4]

The ir spectrum of **1** in chloroform solution showed a hydrogen-bonded OH band at 3000 cm^{-1} and strong absorption at 1739 cm^{-1} due to the carbonyl stretch of α-pyrone.[5] The hydroxyl proton shifts in the nmr spectrum of **1** were relatively independent of the concentration and temperature (Tables I and II), and the molecular weight measurement by vapor pressure osmotic method using chloroform showed that **1** was monomeric in solution.

The ir spectrum in the solid phase (KBr disk) showed absorptions at 2600 cm^{-1} (strong hydrogen-bonded ν_{OH}) and at 1660 cm^{-1} ($\nu_{C=O}$ of γ-pyrone). These data suggest the γ-pyrone structure (**1a**) for the adduct in the solid state, whereas in the liquid phase this adduct may be present predominantly in the form of its tautomeric α-pyrone (**1b**).[6]

(1) H. Hopff and G. Hegar, *Helv. Chim. Acta*, **44**, 2016 (1961).
(2) E. Ziegler and H. Biemann, *Monatsh. Chem.*, **93**, 34 (1962).
(3) F. Haadetzky and E. Ziegler, *ibid.*, **97**, 398 (1966).
(4) M. A. Butt and Y. A. Elvidge, *J. Chem. Soc.*, 4483 (1963).
(5) D. Herbst, W. B. Moro, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 2427 (1959).
(6) Butt and Elvidge[4] discussed the structure of **1** and concluded that it was **1a** on the basis of the nmr ($CDCl_3$) and ir (Nujol); however, their treatment may be inadequate because our observation suggests that the structure of **1** in liquid phase is different from that in the solid.

TABLE I
INFLUENCE OF CONCENTRATION[a]

Concn, %	OH shift, τ
0.7	−2.10
1.2	−2.10
3.3	−2.08
5.3	−1.97

[a] In $CDCl_3$ solution at 50°.

TABLE II
INFLUENCE OF TEMPERATURE[a]

Temp, °C	OH shift, τ
20	−2.10
50	−2.02

[a] In 1.9% $CDCl_3$ solution.

Two pyronopyrone isomers (**3**, mp 252–254°, and **4**, mp 226–228°) were produced by the reaction of carbon suboxide with benzoylacetone under similar conditions. The structure of these compounds were assigned by comparison with 7-substituted pyronopyrones as shown in Table III. The spectrum of **3** indicates conjugation

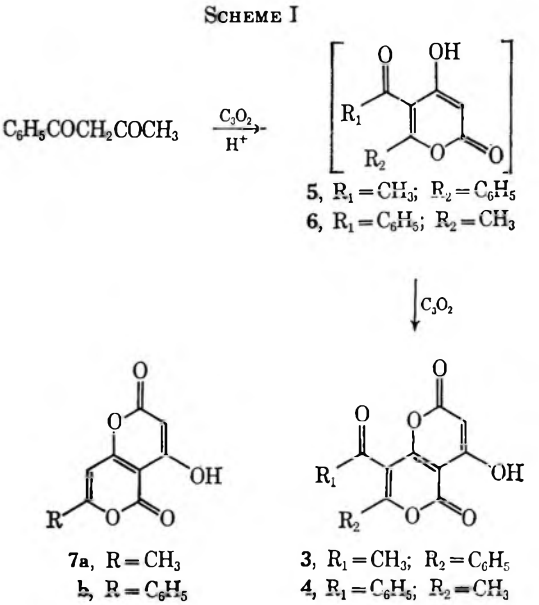
TABLE III
ULTRAVIOLET ABSORPTION MAXIMA

Compd	λ_{max}, mμ (log ϵ), in EtOH
3	245 (4.20), 278 (4.20), 357 (4.16)
4	255 (4.09), 315 (3.77)
7a[a]	270 (3.81), 330 (3.76)
7b[b]	219 (4.33), 247 (4.06)
	280 (4.23), 363 (4.31)

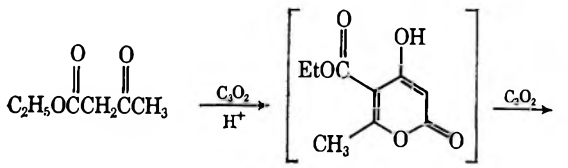
[a] T. Money, I. H. Qureshi, G. B. Webster, and A. I. Scott, *J. Amer. Chem. Soc.*, **87**, 3004 (1965). [b] J. L. Douglas and T. Money, *Can. J. Chem.*, **45**, 1990 (1967).

between pyronopyrone ring and benzene ring. Thus, **3** and **4** can be assigned the structures 8-acetyl-4-hydroxy-7-phenyl-2H,5H-pyrono[3,2-*c*]pyrone and 8-benzoyl-4-hydroxy-7-methyl-2H,5H-pyrono[3,2-*c*]pyrone, respectively (Scheme I).

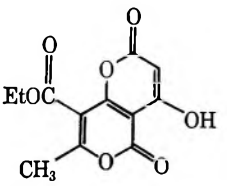
SCHEME I



The reaction of carbon suboxide with ethyl acetoacetate gave the pyronopyrone **9** in a 70% yield. The assignment of **9** is based on uv, ir, and nmr data.

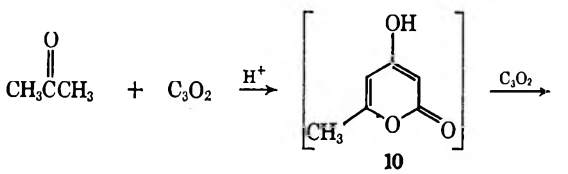


8

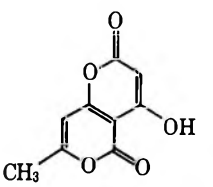


9

The reaction of acetone with carbon suboxide gave pyronopyrone **11** in 8% yield; the corresponding pyrone **10** was not obtained.

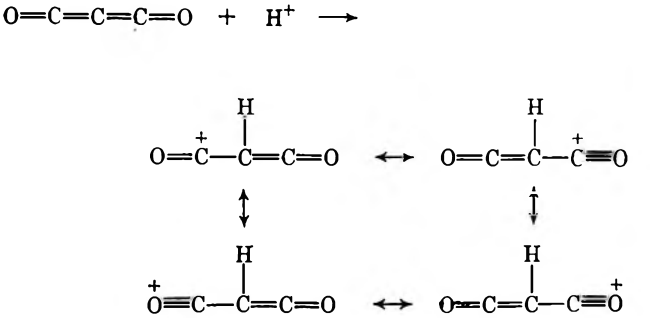


10



11

Although the β-diketones in our experiments were present in significant amounts of their enol form in the reaction mixture,[7] the reaction did not take place without sulfuric acid; a catalytic amount of acid caused the reaction smoothly at room temperature. This suggests that the active species in these reactions may be a protonated carbon suboxide molecule, stabilized by resonance, and that cyclization to form the pyrone ring includes the reaction of enolic β-diketones with protonated carbon suboxide.



The fact that the reaction of acetylacetone gave pyrone and the reaction of the other ketones afforded pyronopyrones under similar conditions suggests that the pyrone (**1b**) may be stabilized by the intramolecular hydrogen bond between 4-hydroxyl and 5-acetyl groups, and may be less reactive toward carbon suboxide than the other intermediates (**5**, **6**, **8**, and **10**). In the cases of **5** and **6**, the intramolecular hydrogen bonding may be unfavorable owing to steric interaction between phenyl and acetyl groups, so that further reaction with carbon suboxide can proceed to yield pyronopyrone. In the case of intermediate **10** from the reaction of acetone, there is no stabilization by hydrogen bonding so that pyronopyrone formation can occur; steric interaction may also interfere with intramolecular hydrogen bonding in intermediate **8** in the reaction with acetoacetic ester.

(7) E. S. Gould in "Mechanism and Structure in Organic Chemistry," Holt-Dryden, New York, N. Y., 1959, p 376.

Experimental Section

Preparation of Carbon Suboxide.—Carbon suboxide was prepared by the pyrolysis[8] of diacetyltartaric anhydride at about 700° and trapped at −78° in a bath of Dry Ice–methanol, and purified by distillation from trap to trap. The identification of carbon suboxide was established by preparation of malonanilide by the reaction of carbon suboxide with aniline.

5-Acetyl-2-hydroxy-6-methyl-4-pyrone (1a).—To a solution of carbon suboxide (0.48 g, 0.007 mol) in dry ether (100 ml) were added slowly acetylacetone (7.0 g, 0.07 mol) and concentrated sulfuric acid (0.02 ml) at −78°. The reaction mixture was maintained at 0–5° for 8 days. Solids (1.0 g, 85%) were separated on a filter and recrystallization from ethyl acetate yielded compound 1a: mp 156–157°; ν_{max}^{KBr} 2600 (-OH), 1695 (C=O), 1660 (C=O), 1600 (C=C), and 1549 cm^{-1} (C=C); $\nu_{max}^{CHCl_3}$ 3000 (-OH), 1739 (C=O), 1660 (C=O) and 1525 cm^{-1} (C=C); λ_{max}^{EtOH} 225 mμ (log ε 4.0) and 261 (3.91); nmr ($CDCl_3$) τ 7.39 (s, 3, CH_3), 7.32 (s, 3, CH_3), 4.47 (unresolved, 1, CH=C), and −1.90 (s, 1, OH). The molecular weight was found to be 167 ($CHCl_3$, osmotic method) (calcd for $C_8H_8O_4$, 168.1).

Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.47; H, 4.88.

5-Acetyl-4-hydroxy-6-methyl-2-pyridone (2).—In a 50-ml autoclave were placed the pyrone (1a, 1.0 g) and aqueous ammonia (20 ml, *d* 0.9). The autoclave was heated to 70° and maintained at 70° for 6 hr and at 20° for 3 days. The solvent was evaporated and the residue was triturated with ether. Recrystallization from ethanol yielded compound 2: mp 284–286° dec; yield 0.5 g.

Anal. Calcd for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.41; H, 5.71; N, 8.40.

8-Acetyl-4-hydroxy-7-phenyl-2H,5H-pyrono[3.2-*c*]pyrone (3) and 8-Benzoyl-4-hydroxy-7-methyl-2H,5H-pyrono[3,2-*c*]pyrone (4).—To a solution of carbon suboxide (2.2 g, 0.032 mol) in absolute ether (30 ml) were added at −78° benzoylacetone (7.9 g, 0.049 mol) and concentrated sulfuric acid (0.05 ml). The reaction mixture was maintained at 0–5° for 1 day, and then the solids were filtered and recrystallization from benzene gave compound 3: mp 252–254°; yield 0.55 g (12%); ν_{max}^{KBr} 1750 [-C(=O)O-, α-pyrone], 1690 [-C(=O)O-, α-pyrone], 1640 cm^{-1} (C=O); λ_{max}^{EtOH} 245 mμ (log ε 4.20), 278 (4.20), 357 (4.16); enolic OH group (by $FeCl_3$ test). The molecular weight was found to be 285 ($CHCl_3$, osmotic method) (calcd for $C_{16}H_{10}O_6$, 298.

Anal. Calcd for $C_{16}H_{10}O_6$: C, 64.43; H, 3.08. Found: C, 64.32; H, 3.27.

An additional 0.34 g (7%) of compound 4, mp 226–228°, was obtained by repeated crystallization from the mother liquor. The infrared spectrum of 4 showed ν_{max}^{KBr} 1750 [-C(=O)O-, α-pyrone], 1702 [-C(=O)O-, α-pyrone], 1670 cm^{-1} (C=O). The ultraviolet spectrum of 4 showed λ_{max}^{EtOH} 255 mμ (log ε 4.09), 315 (3.77). The nmr spectrum of 4 (in $CDCl_3$) showed τ 2.5 (m) Ph, 4.5 (s) C=CH, 7.7 (s) CH_3. 4 had an enolic OH group (by $FeCl_3$ test). The molecular weight was found to be 290 ($CHCl_3$, osmotic method) (calcd for $C_{16}H_{10}O_6$, 298).

Anal. Calcd for $C_{16}H_{10}O_6$: C, 64.43; H, 3.08. Found: C, 64.53; H, 3.37.

8-Ethoxycarbonyl-4-hydroxy-7-methyl-2H,5H-pyrono[3,2-*c*]-pyrone (9).—To a solution of carbon suboxide (1.1 g, 0.016 mol)

(8) E. Ott, *Ber.*, **47**, 2388 (1914).

in dry ether (100 ml) were added ethyl acetoacetate (10 g, 0.077 mol) and concentrated sulfuric acid (0.02 ml) at −78 . The reaction mixture was maintained at 0–5° for 10 days. The crystals (1.5 g, 70%) were isolated, and recrystallization from ethyl acetate gave compound 7: mp 142–143°; ν_{max}^{KB} 1763 (C=O), 1700 (C=O), 1689 cm^{-1} (C=O); λ_{max}^{EtOH} 268 mμ (log ε 4.05), 329 (3.74); nmr ($CDCl_3$) τ 8.57 (t, 3, $-CH_2CH_3$), 7.42 (s, 3, $-CH_3$), 5.54 (q, 2, $-CH_2CH_3$), 4.35 (s, 1, C=CH–); enolic –OH group (by $FeCl_3$ test). The molecular weight was found to be 280 ($CHCl_3$, osmotic method) (calcd for $C_{12}H_{10}O_7$, 266).

Anal. Calcd for $C_{12}H_{10}O_7$: C, 54.14; H, 3.79. Found: C, 53.89; H, 3.94.

4-Hydroxy-7-methyl-2H,5H-pyrono[3,2-*c*]pyrone (11).—In a 200-ml autoclave were placed acetone (40.7 g, 0.72 mol), carbon suboxide (8.7 g, 0.12 mol), dry ether (110 ml), and concentrated sulfuric acid (0.3 ml). The autoclave was maintained at 20° for 14 days, and heated to 60° for 1 day. The resinoid was separated on a filter, and 1.0 g (8%) of solid was extracted with ether from the resinoid. The recrystallization from ethyl acetate gave compound 8: mp 225°; ν_{max}^{KBr} 1762 (C=O), 1695 (C=O), 1638 cm^{-1} (C=O); λ_{max}^{EtOH} 271 mμ (log ε 4.17), 330 (3.93); nmr ($CDCl_3$) τ 7.60 (s, 3, CH_3), 4.50 (s, 1, C=CH), 3.78 (s, 1, C=CH). The molecular weight found to be 180 (Rast method) (calcd for $C_9H_6O_5$, 194.1).

Anal. Calcd for $C_9H_6O_5$: C, 55.68; H, 3.14. Found: C, 55.81; H, 3.04.

Registry No.—Carbon suboxide, 12076-43-6; acetylacetone, 123-54-6; benzoylacetone, 93-91-4; ethyl acetoacetate, 141-97-9; acetone, 67-6-41; **1a**, 19926-37-5; **2**, 1198-08-9; **3**, 17313-47-2; **4**, 19926-40-0; **9**, 19926-41-1; **11**, 4860-88-2.

Novel Formation of the Benzil from 2-(Dimethylaminomethyl)benzaldehyde under Benzoin Condensation Conditions[1]

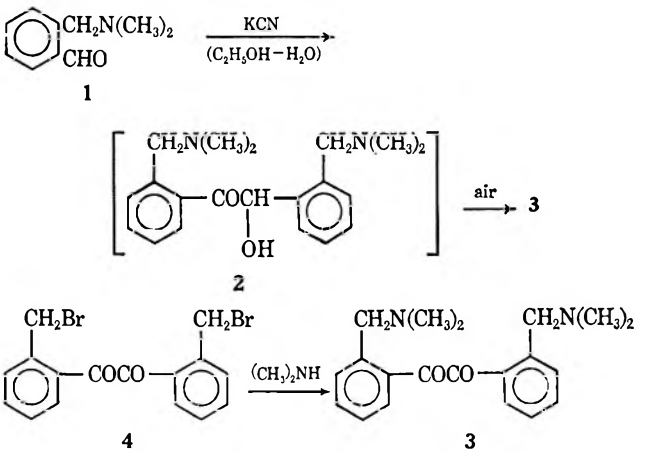
EARL M. LEVI AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina 27706

Received December 23, 1968

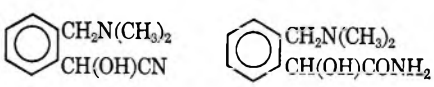
Although many examples of the benzoin condensation of an aromatic aldehyde by an alkali cyanide in ethanol–water have been reported,[2] none appears to have been accompanied by oxidation to form the benzil instead of the benzoin. In fact, subsequent conversion of the benzoin into the benzil has generally been effected by moderate or strong oxidizing agents.[3]

We have found that 2-(dimethylaminomethyl)benzaldehyde (**1**) undergoes the benzoin condensation under the usual conditions to form directly 2,2′-bis(dimethylaminomethyl)benzil (**3**) in about 50% yield. Presumably diaminobenzoin **2** was an intermediate which was oxidized by air. The starting compound **1** was prepared from the reaction of the lithium derivative of benzyldimethylamine with N,N-dimethylformamide and from the Grignard reagent of 2-bromobenzyldimethylamine and triethyl orthoformate. The first method is the one of choice. The diaminobenzil **3** was independently synthesized from 2,2′-dimethylbenzil through the dibromo derivative **4** (see Experimental Section).



The structure of the diaminobenzil **3** was supported by analysis and absorption spectra. The infrared spectrum showed a carbonyl peak at 5.98 μ but no hydroxyl peak. The nmr spectrum showed the methyl protons and methylene protons as singlets and an aromatic proton multiplet in the ratio 12:4:8. The mass spectrum showed the highest peak at *m/e* 324, with the base peak at *m/e* 162, and a reasonably intense peak at *m/e* 58 [$(CH_3)_2N^+{=}CH_2$] as might be expected for a benzil[4a] and for a benzyldimethylamine.[4b]

That diaminobenzoin **2** was an intermediate was supported by effecting the reaction under nitrogen in the absence of air. The resulting crude product evidently consisted of mainly **2** as indicated by its nmr spectrum, which also showed the presence of very little **3**. Some of the cyanohydrin **5** may have been present. Recrystallization of this crude product from hot ethanol afforded diaminobenzil **3** in almost quantitative yield.



In addition to the yellow diaminobenzil **3**, there was isolated from the reaction mixture a white solid which was shown by high resolution mass spectrometry and elemental analysis to have the elemental composition $C_{11}N_{16}N_2O_2$. Its infrared and nmr spectra are consistent with hydroxyaminoamide **6**, which would be the partial hydrolysis product of the cyanohydrin **5**. Cyanohydrins are known to be intermediates in the benzoin condensation[5] but formation of a hydroxyamide such as **6** as a by-product appears not to have been reported previously. As might be expected, the methylene group of **6** showed geminal coupling, having an AB pattern in its nmr spectrum which is characteristic of methylene groups *ortho* to an asymmetric center.[6]

(1) Supported by Public Health Service Grant No. CA-04455 from the National Cancer Institute.

(2) (a) W. S. Ide and J. S. Buck, *Org. Reactions*, **4**, 60 (1948); (b) C. D. Shacklett and H. A. Smith, *J. Amer. Chem. Soc.*, **75**, 2655 (1953).

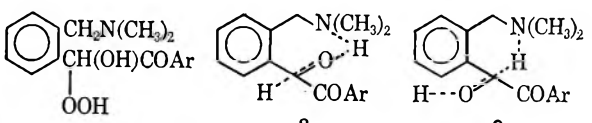
(3) (a) R. Adams and C. S. Marvel, *Org. Syn.*, **1**, 25 (1921); (b) J. van Alphen, *Rec. Trav. Chim. Pays-Bas*, **48**, 1112 (1929); (c) B. Klein, *J. Amer. Chem. Soc.*, **63**, 1474 (1941); (d) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, England, 1957, p 715; (e) H. T. Clarke and E. E. Dreger, *Org. Syn.*, **6**, 6 (1926); (f) E. Fischer, *Ann. Chem.*, **211**, 214 (footnote) (1882).

(4) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day Inc., San Francisco, Calif., 1967, p 138; (b) pp 297–309.

(5) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp 394–397.

(6) J. C. Randall, R. L. Vaulx, M. E. Hobbs, and C. R. Hauser, *J. Org. Chem.*, **30**, 2035 (1965); J. C. Randall, J. J. McKleskey, III, P. Smith, and M. E. Hobbs, *J. Amer. Chem. Soc.*, **86**, 3229 (1964).

The mechanism of the air oxidation of intermediate diaminobenzoin **2** to form diaminobenzil **3** has not been established. We suggest that the function of the tertiary amino group in **2** is to weaken the C–H bond of the methine hydrogen *via* hydrogen bonding in an intermediate such as **8** or **9** and thus facilitate either the formation of the peroxide **7** or transfer of the hydrogen atom to oxygen to form an intermediate radical. A peroxide similar to **7** has been demonstrated to be an intermediate in the air oxidation of benzaldehyde.[7] In addition, hydride transfer from **2** to **1** to form the corresponding amino alcohol and **3** is possible since our material balance accounted for only 53–63%. However, in contrast to our observations, such a mechanism would not require the presence of air.



7 **8** **9**

Although this air oxidation of a benzoin to form a benzil under benzoin condensation conditions appears to be novel, air oxidation of benzoin in the presence of the relatively strong base, alcoholic alkali, has been reported.[8] We have observed that benzoin fails to undergo noticeable air oxidation in the presence of benzyldimethylamine under the usual benzoin condensation conditions; apparently an intramolecular mechanism, as indicated in **8** or **9**, is required for facile autoxidation.

It should be mentioned that the present method of synthesis of aminoaldehyde **1** appears to be more convenient than that reported previously, which involved several steps; the last step of the earlier synthesis involved ozonolysis of 2-(dimethylaminomethyl)styrene.[9]

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord. Nmr spectra were taken on a Varian A-60 instrument operating at 60 MHz and are reported relative to tetramethylsilane as internal standard.[10] Mass spectra were obtained on an Associated Electrical Industries MS-902 spectrometer operated at 70 eV.[11] Ether was dried at reflux over lithium aluminum hydride and was used freshly distilled. Anhydrous magnesium sulfate was employed as the drying agent. Analyses were performed by M-H-W Laboratories, Garden City, Mich.

Preparation of 2-(Dimethylaminomethyl)benzaldehyde (1). A. *n*-Butyllithium Method.—Lithiobenzyldimethylamine (**10**) was prepared under nitrogen from 40.5 g (0.30 mol) of benzyldimethylamine in 300 ml of dry ether and 255 ml of 2.35 *M* (0.60 mol) of *n*-butyllithium in hexane[12] (stirred 22 hr) as described previously.[13] To the stirred solution of **10** was added dropwise 44.4 g (0.63 mol) of freshly distilled N,N-dimethylformamide (vigorous reaction). The resulting solution was stirred for 2 hr, then poured onto a mixture of 125 ml of concentrated HCl and 1 kg of crushed ice. The layers were separated. The cold, aqueous acidic solution was washed twice with ether, and made basic with solid NaOH. The resulting mixture was extracted three times with ether, and the combined ethereal extract was dried. The solvent was removed, and the residue was distilled to give 25.6 g (52%) of 2-(dimethylaminomethyl)benzaldehyde (**1**): bp 112–114° (9.5 mm); bp 122–123° (14 mm) [lit.[9] bp 122–123° (14 mm)]; ir (CCl_4) 5.90 μ (C=O); nmr (CCl_4) δ 2.17 (s, 6 H, $2CH_3N$), 3.67 (s, 2 H, $ArCH_2N$), 7.3–7.4 (m, 3 H), 7.7–7.9 (m, 1 H), 10.30 (2, 1 H, CHO).

B. Grignard Method.—2-Bromobenzyldimethylamine, bp 101–103° (10 mm) [lit.[14] bp 104–106° (9 mm)], was prepared in 71% yield from 140 g (0.64 mol) of o,α-dibromotoluene[15] and 100 g (2.23 mol) of anhydrous dimethylamine in 100 ml of ether (Dry Ice–acetone bath) by a modification of an earlier procedure.[14]

2-Bromobenzyldimethylamine (64.2 g, 0.30 mol) was converted into its Grignard reagent[14] with 9 g (0.4 g-atom) of magnesium in 250 ml of dry ether, and the solution was stirred for 1 hr. Freshly distilled triethyl orthoformate (59.3 g, 0.40 mol) was added slowly, and the resulting mixture was stirred at reflux for 21 hr. Water (500 ml) was slowly added, and the mixture was extracted continuously with ether for 24 hr. The ethereal solution was extracted with 500 ml of 3 *M* HCl. The acidic solution was heated near reflux for 3 hr, then cooled and made basic with solid NaOH. The resulting mixture was extracted with ether. After drying, the ethereal extract was evaporated, and the residue was distilled to give 17.5 g (40%) of benzyldimethylamine (identified by vpc retention time) and 19.5 g (39%) of **1**, bp 104–106° (8 mm); the nmr spectrum was indistinguishable from that of **1** obtained by method A.

Benzoin Condensation of 2-(Dimethylaminomethyl)benzaldehyde (1). A. Under Usual Conditions (in Air).[2b]—A mixture of 19.5 g of aminoaldehyde **1**, 2.5 g of KCN, and 15 ml each of 95% EtOH and water was refluxed (solution) for 2 hr. The solution was cooled overnight, and the resulting precipitate was removed by filtration to give 5.72 g of yellow needles of 2,2′-bis(dimethylaminomethyl)benzil (**3**), mp 136–145°. The filtrate was refluxed with an additional 3.5 g of KCN for another 2 hr, chilled, and seeded. The resulting precipitate was again removed by filtration to give 2.19 g of yellow needles of **3**, mp 146–151°. The filtrate was extracted with ether and the solvent was removed from the ethereal extract. The residue was steam distilled to give, after recrystallization from 95% EtOH, 1.30 g of **3** as yellow needles, mp 148–151°. The total yield of **3** was 9.21 g (50%). Four crystallizations from EtOH gave an analytical sample: mp 149.5–150.5°; ir (CCl_4) 5.98 μ (C=O); nmr (CCl_4) δ 2.10 (s, 12 H, $4NCH_3$), 3.63 (s. 4 H, $2ArCH_2N$), 7.3–7.6 (m, 8 H); mass spectrum, *m/e* (relative intensity) 324 (25), 250 (26), 207 (10), 179 (18), 178 (11), 163 (13), 162 (100), 132 (11), 119 (43), 91 (48), 58 (16).

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.24; H, 7.64; N, 8.67.

Concentration of the mother liquor obtained from crystallization of the final crop of **3** afforded apparently hydroxy-2-(dimethylaminomethyl)phenylacetamide (**6**, white needles): mp 180–181°; ir ($CHCl_3$) 2.85, 2.88, 2.95, and 5.95 μ; nmr ($CDCl_3$) δ 2.23 (s, 6 H, $2NCH_3$), 3.20 (d, 1 H, J = 13 Hz) and 3.80 (d, 1 H, J = 13 Hz) ($ArCH_2N$), 5.13 [s, 1 H, ArCH(OH)CO], 6.2–6.6 (b, 1 H, OH), 7.1–7.4 (m, 4 H), 7.7–8.0 (b, 2 H, NH_2); mass spectrum, *m/e* (relative intensity) 208 (1), 165 (30), 164 (92), 163 (98), 162 (13), 135 (15), 134 (15), 120 (32), 119 (100), 118 (58), 92 (15), 91 (68), 90 (11), 65 (15), 58 (74), 46 (45), 44 (51).

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45; mol wt, 208.1212. Found: C, 63.24; H, 7.91; N, 13.56; mol wt (mass spectroscopy), 208.1216.

B. Under Nitrogen.—A solution of 12 g of KCN in 25 ml of water was added to a solution of 16.3 g of aminoaldehyde **1** in 75 ml of 95% EtOH which had been flushed with oxygen-free nitrogen[16] for 2 hr. Nitrogen was passed through the mixture for 0.5 hr and the mixture was refluxed for 2 hr (solution) under a blanket of nitrogen. After cooling, the solution was diluted with 200 ml of water, and nitrogen was bubbled through the resulting mixture for 0.5 hr. The mixture was kept at −20° for 3 days, and then filtered to give 6.87 g of a light yellow solid: nmr ($CDCl_3$) δ 2.03 (s), 2.12 (s), 2.17 (s), 2.25 (s), many small peaks

(7) Reference 5, p 708.

(8) L. Michaelis and E. S. Fetcher, *J. Amer. Chem. Soc.*, **60**, 1246 (1937).

(9) H. W. Bersch and R. Meyer, *Arch. Pharm.*, **287**, 613 (1954).

(10) In nmr descriptions: s = singlet, d = doublet, m = multiplet, b = broad.

(11) We thank Dr. David Rosenthal for the mass spectral determinations, which were done at the Research Triangle Mass Spectrometry Center supported by Special Facility Grant No. FR-00330-01, National Institutes of Health.

(12) Obtained from Alfa Inorganics, Inc., Beverly, Mass.

(13) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).

(14) F. N. Jones and C. R. Hauser, *ibid.*, **27**, 4389 (1962).

(15) F. DeTar and L. A. Carpino, *J. Amer. Chem. Soc.*, **78**, 475 (1956).

(16) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 393.

2.5–3.1, 3.53 (d, J = 4 Hz), and AB system with doublets centered at 3.75 and 4.17 (J = 12 Hz), 5.97 (d, J = 4 Hz), 7.0–7.3 (m). This crude product was dissolved in 150 ml of absolute EtOH at room temperature, and 700 ml of water was added to give yellow solid, mp 102–130°, the nmr spectrum of which was almost indistinguishable from that of pure **3**. Recrystallization from hot 95% EtOH gave pure **3**, mp and mmp 149–151°.

Independent Synthesis of Diaminobenzil 3.—A solution of 32.76 g (0.205 mol) of bromine in 100 ml of CCl_4 was added dropwise during 4 hr to a hot, stirred solution of 23.8 g (0.1 mol) of 2,2′-dimethylbenzil[2b] in 500 ml of CCl_4 containing a few crystals of benzoyl peroxide; during this time, the reaction mixture was irradiated with a2 50-W sun lamp. The product crystallized on cooling (ice bath) and was filtered. It was then washed with cold CCl_4 to give 17.32 g (44%) of the crude 2,2′-di(bromomethyl)benzil (**4**): mp 145–155° (decomposes to a black tar); ir ($CHCl_3$) 5.97 μ (C=O); nmr ($CDCl_3$) δ 5.04 (s, 4 H, 2Ar-CH_2Br), 7.2–7.7 (m, 8 H). The nmr spectrum of the filtrate obtained on removing crude **4** showed peaks indicating the presence of non-, mono-, and dibrominated methyl groups in the mixture of benzils remaining. Three crystallizations of **4** from CCl_4 gave a sample: mp 155–156° (decomposes to a black tar); mass spectrum, m/e (relative intensity) 398 (0.08), 396 (0.14), 394 (0.08), 318 (0.2), 317 (1.2), 316 (1.7), 315 (1.2), 314 (1.4), 200 (10), 199 (100), 198 (10), 197 (100), 119 (15), 118 (93), 90 (37), 89 (19). The sample was not analytically pure.

The crude dibromobenzil **4** (1.25 g, 3.2 mmol) was added to anhydrous dimethylamine (*ca.* 40 ml) and the mixture stirred at reflux (Dry Ice–acetone condenser) for 2 hr. The mixture was poured into water, dilute $NaHCO_3$ solution was added, and the aqueous mixture was extracted with ether. The ethereal extracts were dried and evaporated. The residue was recrystallized from 95% EtOH to give 0.72 g (70%) of **3** as yellow needles, mp and mmp 149–151°. The infrared spectra of the two samples were indistinguishable.

Failure of Autoxidation of Benzoin in the Presence of a Tertiary Amine.—A solution of benzoin (2.12 g, 0.01 mol), KCN (0.5 g), and benzyldimethylamine (1.35 g, 0.01 mol) in 95% EtOH (40 ml) was refluxed for 24 hr, cooled, and the precipitate (white needles) was filtered to give 1.30 g (62%) of benzoin, mp and mmp 132–133°. Vpc of the mother liquor showed no peak for benzil, but did show a peak for benzoin. Probably more benzoin could have been recovered from the mother liquor.

Registry No.—**1**, 19886-78-3; **3**, 19922-49-7; **4**, 19886-79-4; **6**, 19886-80-7; benzoin, 119-53-9.

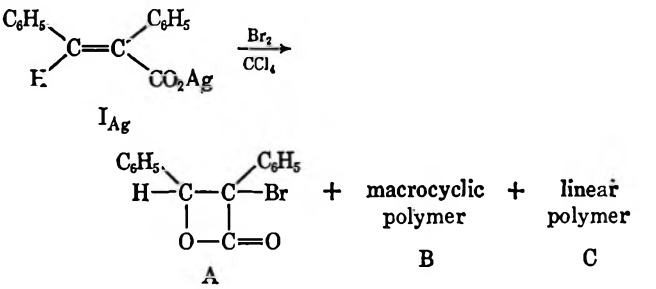
Bromination of Silver and Sodium Stilbenecarboxylates

CHARLES C. PRICE AND HARRY W. BLUNT[1]

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

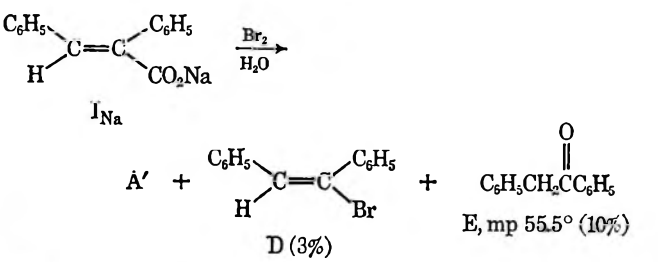
Received September 26, 1968

In 1957, Berman and Price[2] reported that sodium *cis*- and *trans*-stilbene-α-carboxylates were brominated to give good yields of the corresponding bromostilbenes. We have been unable to confirm this report, nor have others.[3,4] Our further studies have, however, led to the isolation of bromo-β-lactone A and its macrocyclic (B) and linear polymer C which we wish to report here.



I_{Ag} A

The product obtained from the sodium salt in water almost certainly included a β-lactone (ir absorbance at 1850 cm^{-1}) but it could not be separated by chromatography. Unlike β-lactone A, it failed to produce macrocyclic polymer B on warming in methanol, suggesting A′ may be a geometric isomer of A.

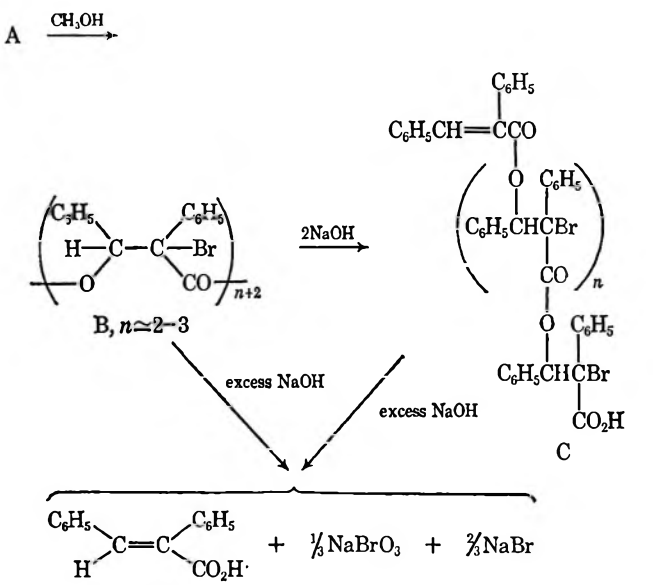


I_{Na}

The *trans* salts (II_{Ag} and II_{Na}) gave essentially the same results, except that *no* bromostilbene was isolated from II_{Na} and the recovered acid was I, *not* II.

The formation of a bromolactone is analogous to the similar reaction reported for dimethylmaleic acid.[5] The lactone, readily identified by its ir absorbance at 1850 cm^{-1}, was obtained as an oil.

The macrocyclic polymer was readily converted into a linear polymer by 2 equiv of base. On more vigorous conditions, both polymers were degraded to I and sodium bromate,[6] with consumption of 2 equiv of base per unit. The cleavage of any one of the ester links in B could occur more readily than further reaction of these links in C due to ring strain in B, more favorable



(1) From the Ph.D. Dissertation of H. W. Blunt, 1965.

(2) J. D. Berman and C. C. Price, *J. Amer. Chem. Soc.*, **79**, 5474 (1957).

(3) B. B. Jarvis and W. Protz, Department of Chemistry, University of Maryland, College Park, Md.; *J. Org. Chem.*, **33**, 874 (1968).

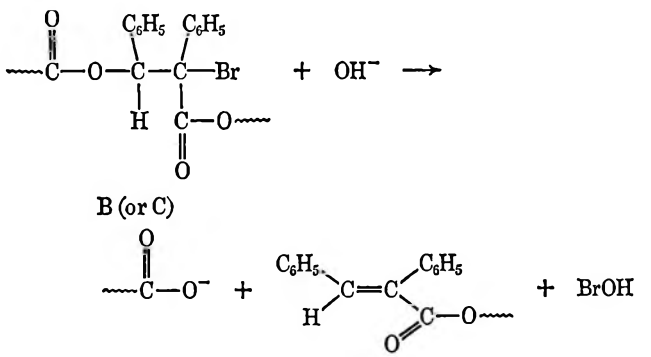
(4) W. Brown and S. Jankowski, Argonne National Laboratories, Argonne, Ill., private communication.

(5) D. S. Tarbell and P. D. Bartlett, *J. Amer. Chem. Soc.*, **59**, 408 (1937).

(6) A. G. Cotton and G. Wilkinson ["Advanced Inorganic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1962] report the equilibrium constant (K = 10^{15}) heavily favors disproportionation of hypobromite to bromate and bromide.

orientation in B, or the negative charge acquired by C in base.

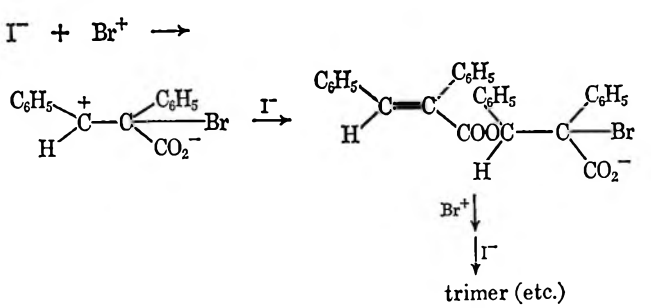
So far as we are aware the elimination of the elements of hypobromous acid from a bromohydrin ester has not been previously reported. There are a number of features of the structures of B and C which would favor this course for the reaction in these cases. First of all, normal saponification of the ester would be highly sterically hindered since hydroxyl attack at the ester carbon expands this group to tetrahedral geometry, whereas attack on bromine could be linear with the C–Br bond and would certainly be further from the hindered site because of the larger radius of bromine than carbon. Second, an elimination reaction would be favored not only by relief of steric strain but by the resonance stabilization of the resulting double bond, conjugated to a carbonyl group and two phenyl groups. We therefore formulate the reaction as involving nucleophilic attack by base on bromine followed by (or concurrent with) loss of the β-carboxylate ion.[7] It is



B (or C)

of interest to point out that this reaction occurred much more readily to open the ring in B than to degrade further the linear polymer C thus formed to I.

In addition to formation of linear polymer C by ring opening of macrocyclic lactone, it may be formed during bromination by the following sequence of reactions.



The various products had readily differentiated ir spectra in the carbonyl frequency. The β-lactones, A and A′, each had a strong sharp band at 1850 cm^{-1}. The macrocyclic polymer B was characterized by a strong band at 1760 cm^{-1}. The linear polymer C had bands at 1750 (unconjugated) and 1720 cm^{-1} (conjugated) while the deoxybenzoin E had absorption at 1690 cm^{-1}.

In a study similar to ours on bromination of I_{Na} and II_{Na} in water, Jarvis and Protz[3] obtained deoxybenzoin and *cis*- and *trans*-stilbenes, by glpc, in yields appreciably better than those which we obtained by column chromatography. They did not detect the β-lactone (A′) which may have decarboxylated on heating to the stilbenes.

Experimental Section[8]

cis- and *trans*-stilbenecarboxylic acids were prepared by the method of Fieser.[9] The silver salts were prepared as before,[2] dried under vacuum at 50–60°, and stored in a darkened desiccator. The carbon tetrachloride was dried over molecular sieves for 24 hr.

Bromination of I_{Ag} (10 g) dispersed in 300 ml of CCl_4 was accomplished by adding it and 5 g of Br_2 in 100 ml of CCl_4 to 500 ml of CCl_4 with stirring. After 3 hr the pale yellow mixture was filtered, washed with dilute sodium bisulfite, then with dilute sodium bicarbonate, and concentrated to 50 ml at 35–38°. The solution was charged to a 3.5 × 20 cm column of Florisil. Elution with 250 ml of CCl_4 gave a mixture of A (ν_{CO} 1850 cm^{-1}) and B (ν_{CO} 1760 cm^{-1}), converted entirely into B, mp 125–132°, by dissolving in hot methanol.

Anal. Calcd for $(C_{15}H_{11}O_2Br)_n$: C, 59.42; H, 3.66; Br, 26.35. Found: C, 59.57; H, 3.78; Br, 26.58.

Elution with 250 ml of 3:1 benzene–methanol gave linear polymer C. Acidification of the bicarbonate wash precipitated I, mp 173–174°. Results of three experiments are summarized in Table I.

TABLE I

REACTION OF SILVER *cis*-STILBENECARBOXYLATE WITH BROMINE IN CCl_4

	Amt, %				M_n of C	
Expt	I	A	B	C	Titration[g]	Vapor osmtry[h]
1[a]	20		26	12[d]	1050	114
2[b]	6	18	6	30[e]	1330	1400
3[c]	1	24	9	23[f]	2430	2600

[a] I_{Ag} air dried. [b] I_{Ag} vacuum dried at 50° for 48 hr. [c] Same as footnote *b*, then ground and redried for 25 hr additional. [d] *Anal.* Calcd for C (n = 2) (1134): C, 63.56; H, 4.00; Br, 21.15. Found: C, 63.41; H, 4.24; Br, 20.03. [e] *Anal.* Calcd for C (n = 3) (1436): C, 62.56; H, 3.90; Br, 22.35. Found: C, 61.98; H, 4.26; Br, 24.07. [f] *Anal.* Calcd for C (n = 2 + Br_2): C, 554.9; H, 3.39; Br, 31.26. Found: C, 56.03; H, 3.61; Br, 31.14. [g] By alkaline titration in DMSO, assuming two titratable acid groups. The titration and osmometric molecular weights would also be in agreement for one titratable acid group if the polymer molecules were dimeric in benzene (through association *via* carboxylic acid end groups). [h] By Mechrolab vapor osmometer in benzene.

One sample of linear polymer C (2.3 g) was fractionated from 200 ml of CCl_4 by adding 300 ml of methanol to precipitate 0.61 g of polymer, mp 168–233°. Removal of CCl_4 by evaporation and further methanol addition gave additional fractions of 0.42 g (mp 128–141°), 0.37 g (mp 105–129°), and 0.58 g (mp 95–115°), as well as 0.09 g of I (mp 172°). This "linear" polymer C showed broadened nmr absorption at δ 5.6 and 6.8 ppm.

Bromination of II_{Ag} (15 g) with 7.5 g of bromine in 300 ml of CCl_4 for 3 hr at room temperature gave 1.1 g of I from the bicarbonate wash, 4.55 g of a mixture of A and B from CCl_4 elution of the Florisil column, and C from methanol–benzene elution.

(7) A similar nucleophilic attack on bromine in vicinal dibromide by benzhydryl anion has recently been suggested by W. C. Kofron and C. R. Hauser, *J. Amer. Chem. Soc.*, **90**, 4126 (1968).

(8) All melting points are uncorrected. Analyses were by Dr. A. Bernhardt, Max Planck Institute, West Germany.

(9) L. F. Fieser, *J. Chem. Educ.*, **31**, 293 (1954).

Purification of A.—A crude sample of 4.55 g of A was dissolved in 10 ml of warm CCl_4 and applied to the Florisil column. Elution with five 25-ml portions of low-boiling petroleum ether (bp 30–60°) gave 3.0 g of oil, ν_{CO} 1850 cm^{-1}, still containing a small amount of B (by ir): $n^{26}D$ 1.6124; d^{26} 0.833. It solidified to a glass at −70° and the nmr spectra showed sharp singlets at δ 5.95 and 7.10 ppm in the proper 10:1 ratio.

Anal. Calcd for $C_{15}H_{11}O_2Br$: C, 59.42; H, 3.66; Br, 26.35. Found: C, 59.60; H, 3.34; Br, 26.30.

The molecular weight by vapor osmometer was 350 g/mol, compared with the calculated value of 303.

Conversion of A into B.—When a boiling solution of 2 g of A in 25 ml of methanol was chilled in a Dry Ice–acetone bath, a 1.8 g yield of B (mp 125–132°, ν_{CO} 1760 cm^{-1}) was obtained. The nmr spectra showed broadened singlets at δ 5.8 and 7.0 ppm in the proper ratio.

Anal. Calcd for $(C_{15}H_{11}O_2Br)_4$: C, 59.42; H, 3.66; Br, 26.35; mol wt, 1212. Found: C, 59.33; H, 3.80; Br, 26.49; mol wt, 1380.

The polymer was amorphous by X-ray diffraction.

Alkaline Titration of B.—While there was no evidence for acid end groups in B (from ir), samples in DMSO could be titrated with 0.21 *N* NaOH. Assuming conversion of B into C 2 mol of NaOH would be required. The observed molecular weight from titration was 1186, comparing favorably to the 1380 determined by vapor osmometry and the theoretical value for $n = 2$ of 1212. Acidification after titration precipitated 98% of the initial sample as C.

Anal. Calcd for $C_{60}H_{45}O_8Br_3$: C, 63.56; H, 4.00; Br, 21.15. Found: C, 63.57; H, 4.32; Br, 20.26.

Saponification of B and C.—Weighed samples of B (or C) were refluxed in 100 ml of 1 *N* ethanolic KOH for 40 hr. From back-titration with 1 *N* HCl, two samples of B were found to consume 2.02 and 2.00 equiv of NaOH per monomer unit. For C, 2.24 equiv of NaOH per monomer unit was consumed. After titration, addition of concentrated HCl precipitated I, mp 173–174°, in high yield.

The saponification mixture after refluxing contained a white crystalline precipitate. In one case, this material was collected by filtration, dissolved in water, and treated with KI and starch. Acidification produced a dark blue color. For two polymer samples, the precipitate was dissolved in water, acidified, treated with KI, and titrated with 0.1 *N* thiosulfate, showing 11.5 and 11% of the calculated titer. The ethanol filtrate when treated similarly showed only an additional 2.5%. Presumably the majority of the hypobromite was consumed by oxidizing the ethanol solvent, a reaction which can be used to prepare bromoform.

Bromination of I_{Na} was accomplished by dissolving 10 g of I and 1.6 g of NaOH in 200 ml of water followed by dropwise addition of 6.4 g of bromine with stirring at 50°. After cooling, the reaction mixture was extracted with three 100-ml portions of ether. The ether was washed with 1% sodium bisulfite then 2% alkali, 5% hydrochloric acid, and water. Drying and evaporation left 7.03 g of yellow oil, ν_{CO} 1850 and 1690 cm^{-1}. The ratio of A to E could be approximated from the ir spectrum and the elementary analysis of the mixture could then be rationalized on the basis of the composition indicated.

Anal. Calcd for 63.5% A, 14.1% D, 22.2% E: C, 66.08; H, 4.12; Br, 21.18. Found: C, 66.21; H, 4.42; Br, 21.16.

No separation was effected on Florisil, but on Woelm alumina (1.5 × 5 in) elution with petroleum ether (bp 30–60°) gave 0.32 g (3%) of D, identified by uv and ir spectra. Elution with CCl_4 gave 0.45 g (10%) of E (ν_{CO} 1690 cm^{-1}, mp 53–55°) after recrystallization from methanol. The lactone unfortunately could not be eluted from the alumina column.

Bromination of II_{Na} (10 g) similarly gave 1.12 g (25%) of E (from 4.6 g of crude neutral oil showing ν_{CO} 1850 and 1690 cm^{-1}). Acidification of the alkaline extract gave 2.0 g of I. Under conditions which completely converted the lactone A from silver salt into macrocyclic polymer B, the β-lactone (A′) obtained from sodium salt bromination was stable in boiling methanol, yielding no precipitate on cooling, and leaving an oil on evaporation with the same ratio of ir absorption at 1850 and 1690 cm^{-1} as before heating in methanol.

Registry No.—I_{Ag}, 19926-54-6; I_{Na}, 15352-96-2; II_{Ag}, 19926-56-8; II_{Na}, 15352-97-3; A, 19926-34-2; C, 19926-35-3.

Enol Esters. IX.[1] The Use of Isopropenyl Esters as Acylation Agents. A Convenient Synthesis of Acyl Fluoride

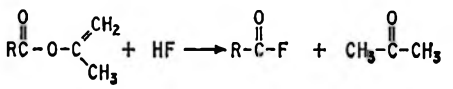
EDWARD S. ROTHMAN, GORDON G. MOORE, AND SAMUEL SEROTA

Eastern Utilization Research and Development Division,[2] Philadelphia, Pennsylvania 19118

Received August 30, 1968

Isopropenyl stearate, I, the stearoylated enol of acetone, is a versatile stearoylating agent. Its high degree of acylation activity is very probably associated with the ease of its thermal cleavage[1] to hexadecylketene. In preceding papers,[1,3] we have described the synthesis of this reactive reagent and have detailed its use in the acylation of amides, imides, and several other compounds. We have now found further examples of the general utility of isopropenyl stearate taken as an example of an enol ester and would like here to present our findings. As will be seen below the reactions are general enol ester reactions and not limited solely to isopropenyl stearate.

When a stream of hydrogen fluoride is passed into an isopropenyl ester (whether neat or in solution in dry



ether) acetone is liberated leaving behind a residue, or a solution of, acyl fluoride. This acid fluoride synthesis was carried out in four aliphatic examples chosen for variation in chain length using isopropenyl acetate, octanoate, octadecanoate, and azelate esters. The acylated products are formed cleanly in high yield. The method offers advantages over the procedure of Olah and Kuhn,[4a] who found that, when they used anhydrides as starting materials, only those derived from C_2 or C_3 acids reacted with hydrogen fluoride fast enough at hydrogen fluoride reflux temperature for preparative utility. These authors prefer to use acid chlorides at −10 to +5°. The present procedure for acyl fluoride preparation does not require the intermediary preparation of acid chloride,[4b] but it should be noted that, if desired for other purposes, acyl chlorides may be similarly prepared uncontaminated by reagents used in their preparation by using hydrogen chloride gas in place of hydrogen fluoride. This acyl chloride synthesis compares well[5] with existing literature procedures using phosphorus trichloride, thionyl chloride,[6] or oxalyl chloride[7] in simplicity of operation, in yield, and particularly in purity of product.

(1) For the previous paper in this series, see E. S. Rothman, *J. Amer. Oil Chem. Soc.*, **45**, 189 (1968).

(2) Agricultural Research Service, U. S. Department of Agriculture.

(3) E. S. Rothman, S. Serota, and D. Swern, *J. Org. Chem.*, **29**, 646 (1964).

(4) (a) G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, **82**, 2380 (1960); *J. Org. Chem.*, **26**, 237 (1961). (b) F. Seel and J. Langer, *Chem. Ber.*, **91**, 2553 (1958).

(5) Because of the importance to the food industry we anticipate that isopropenyl stearate will become a commercially available bulk chemical.

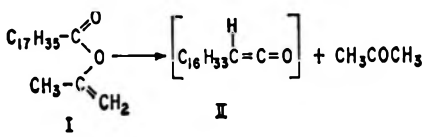
(6) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1658 (1959).

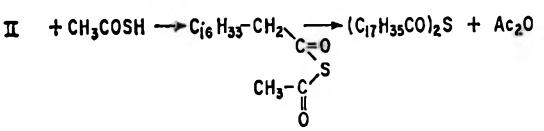
(7) H. E. Kenney, G. Maerker, and E. T. Donahue, *J. Amer. Oil Chem. Soc.*, in press.

Stearoyl fluoride is a crystalline solid melting at 34° and may be distilled without decomposition at 130° at 0.05 Torr. It will be noted that the fluoride melts higher than the 22° melting stearoyl chloride and does not decompose with loss of hydrogen halide during redistillations as does, to a degree, stearoyl chloride.

Acetyl fluoride may be prepared by the enol ester procedure, but added technical problems result from the near-coincidence of the boiling points of acetyl fluoride, bp 20°, and hydrogen fluoride, bp 19°. This problem may be avoided by using exactly equivalent amounts of isopropenyl acetate and hydrogen fluoride (or a slight excess of the former, bp 97°). The reaction itself is quantitative since the enol ester ir bands completely disappear, and only a separation from acetone, bp 56°, is required. We have found further utility for isopropenyl stearate in SH acylations. Both mercaptans and thiophenols may be stearoylated by this reagent, and often the reactions go at temperatures well below those required for OH or NH acylation. We have prepared phenyl thiostearate from thiophenol, benzyl thiostearate from benzyl mercaptan, isobutyl thiostearate from isobutyl mercaptan, and dodecyl thiostearate from dodecyl mercaptan. The easy preparation of the last-named compound contrasts sharply with the results of Sasin, Schaffer, and Sasin,[8] who reported that dodecyl thiostearate does not form even after 24 hr at 250° by the attempted base-catalyzed interchange reaction between methyl stearate and dodecyl mercaptan.

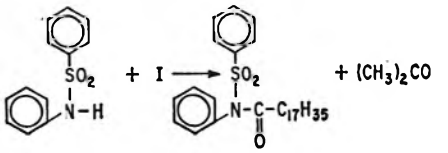
Thiolacetic acid was also successfully stearoylated, but the proximate product acetic stearic thioanhydride was not isolable because of rapid dismutation to stearic thioanhydride and acetic thioanhydride. This change recalls the analogous conversion[9] of acetic–stearic mixed anhydride into acetic and stearic anhydrides. The thioanhydride formulation is based upon the absence of C–O (single bond) infrared absorption bands, and from the reaction of the compound with



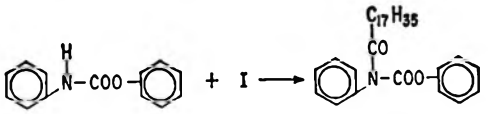


n-butylamine to form N-butylstearamide as the sole crystallizable product. Isopropenyl thiostearate was *not* obtained on reaction with isopropenyl acetate.

Another class of difficult-to-stearoylate compounds yielding easily to the enol ester reagent is the sulfonamide group. Although benzenesulfonamide has two potentially reactive hydrogen atoms attached to nitrogen, only one of these is replaced by the stearoyl group. N-Benzylbenzenesulfonamide and N-phenylbenzenesulfonamide monostearoylate without presenting any difficulties due to hindrance or inductive effects, but sulfanilamide gave only a distearoylated product.



We have also been able to stearoylate several urethan derivatives. As examples, phenyl N-phenylcarbamate, ethyl N-phenylcarbamate, and benzyl N-phenylcarbamate all formed N-stearoyl derivatives.



Products of stearoylation reactions with isopropenyl stearate are given in Table I.

Experimental Section

Stearoyl Fluoride. Procedure A.—Into isopropenyl stearate, 20 g, melted in a Teflon reaction vessel at 110–120° was bubbled a stream of dry hydrogen fluoride for 0.75 hr, after which the vessel was cooled and flushed with dry nitrogen. The infrared spectrum showed complete reaction: ir (CS_2) 1843.4 (C=O) and 1081.7 ± 0.3 cm^{-1} (CF). The product was distilled, bp 130° (0.05 mm) [lit.[4b] bp 169–169.5° (11 mm)], or alternatively directly crystallized from hexane to give flattened needles, mp 34°. In large-scale operations it was possible to do the recrystallization without a special drybox apparatus as long as the material was covered with hexane.

Procedure B.—Into a solution of 20 g of isopropenyl stearate in 350 ml of dry ether was passed a stream of hydrogen fluoride for 2 hr. Infrared analysis showed after solvent evaporation that the residue consisted of pure stearoyl fluoride. Ethyl stearate ir bands were completely absent. The product was completely colorless and the yield quantitative.

Anal. Calcd for $C_{18}H_{35}FO$: C, 75.47; H, 12.32; F, 6.63. Found: C, 75.88; H, 12.53; F, 6.39.

Stearoyl Chloride.—By methods analogus to procedure A (time, 1 hr; temp, 140°) and procedure B but using dry hydrogen chloride gas, pure stearoyl chloride, mp 21.9°, was obtained identical in all respects with an authentic specimen.

Octanoyl Fluoride *via* Isopropenyl Octanoate.—Methylacetylene was condensed to the liquid phase and 60 ml was diluted with 100 ml of methylene chloride at −10°. Mercuric acetate, 16 g, and octanoic acid, 67 g, were added and the mixture was stirred for a minimum of 0.5 hr. Boron trifluoride etherate (0.4 ml) was added and the temperature was maintained at +30°, avoiding higher temperatures leading to anhydride formation and lower temperatures which arrest the reaction completely. After 4 hr stirring the catalyst was neutralized with 4 g of NaOAc and solids were filtered off. The mixture was distilled to give 64 g (70%) of crude ester, bp 63° (0.4 mm). The product was freed of color by a pass through a short Florisil column. The analytical sample of isopropenyl octanoate obtained by redistillation had bp 73° (3 mm).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.75; H, 11.01.

A sample of isopropenyl octanoate, bp 68° (0.1 mm), in a Teflon apparatus was heated to 35° for 1 hr during which time anhydrous hydrogen fluoride was bubbled through. The reaction product was orange in color and contained contaminant octanoic acid as evidenced by ir bands at 1700 cm^{-1}. The mixture was extracted with pentane and the lower, colored layer was discarded. Distillation gave octanoyl fluoride (yield 50%): bp 33° (0.3 mm), 43° (1.7 mm), 162–165° (760 mm) [lit.[4a,10] bp 80° (14 mm)]; ir 1844 (C=O) and 1082 cm^{-1} (CF).

Acetyl Fluoride.—Into a Teflon bottle containing 25 g of commercial isopropenyl acetate was distilled slightly less than an exact equivalent (5 g) of hydrogen fluoride. After a reaction

(8) G. S. Sasin, P. R. Schaeffer, and R. Sasin, *J. Org. Chem.*, **22**, 1183 (1957).

(9) E. S. Rothman, S. Serota, T. Perlstein, and D. Swern, *ibid.*, **27**, 3123 (1962).

(10) G. Olah, S. Kuhn, and S. Beke, *Chem. Ber.*, **89**, 862 (1956).

TABLE I

Substance to be stearoylated	Product obtained	Reaction conditions: Time, min	Reaction conditions: Temp, °C	Mp, °C	Lit. mp	Yield, %
Dodecyl mercaptan	Dodecyl thiostearate	5	125	56–57	54–55[f]	85
Isobutyl mercaptan	Isobutyl thiostearate	5	88	22–23	23[g]	67
Benzyl mercaptan	Benzyl thiostearate	5	120	60.5–61.5	59.5–60[h,i]	80
Thiophenol	Phenyl thiostearate	30	120	38–39.5	39–40[i]	76
Thiolacetic acid	Stearic thioanhydride	60	135	81–81.5	79.5–80.5[j]	95
p-Toluenesulfonamide	N-Stearoyl-*p*-toluenesulfonamide	5	150	97.0–97.2	98–99[k]	80
N-Phenyl-*p*-toluenesulfonamide	N-Phenyl-N-stearoyl-*p*-toluenesulfonamide[a]	7	150	107.5–108.5		85
N-Benzyl-*p*-toluenesulfonamide	N-Benzyl-N-stearoyl-*p*-toluenesulfonamide[b]	7	150	65.0–65.8		64
Sulfanilamide (0.33 equiv)	N,N′-Distearoylsulfanilamide[c]	10	200	135–138		80
Benzyl N-phenylcarbamate	Benzyl N-phenyl-N-stearoylcarbamate[d]	10	160	67–68		87
Phenyl N-phenylcarbamate	Phenyl N-phenyl-N-stearoylcarbamate[e]	15	180	59.5–60.0		45

[a] *Anal.* Calcd for $C_{31}H_{47}NO_3S$: C, 72.47; H, 9.22; S, 6.30. Found: C, 72.76, H, 9.45; S, 6.30. [b] *Anal.* Calcd for $C_{32}H_{49}NO_3S$, C, 72.82; H, 9.36; N, 2.65; S, 6.08. Found: C, 72.81; H, 9.44; N, 2.56; S, 6.28. [c] *Anal.* Calcd for $C_{42}H_{76}N_2O_4S$: C, 71.55; H: 11.26; S, 4.55. Found: C, 71.85; H, 11.26; S, 4.16. [d] *Anal.* Calcd for $C_{32}H_{47}NO_3$: C, 77.85; H, 9.59; N, 2.84. Found: C, 78.05; H, 9.62; N, 2.85. [e] *Anal.* Calcd for $C_{31}H_{45}NO_3$: C, 77.62; H, 9.46; N, 2.92. Found: C, 77.99; H, 9.76; N, 2.76. [f] R. Sasin, *et al.*, *J. Amer. Oil Chem. Soc.*, **35**, 192 (1958). [g] G. S. Sasin, R. Sasin, and N. Capron, *J. Org. Chem.*, **21**, 852 (1956). [h] See ref 8. [i] J. M. Purcell and H. Susi, *Appl. Spectrosc.*, **19**, No. 4, 105 (1965). [j] Y. Hirabayashi, M. Mizuta, and T. Mazume. *Bull. Chem. Soc. Jap.*, **38**, 1099 (1965). [k] G. M. Ford, *Iowa State Coll. J. Sci.*, **12**, 121 (1937); *Chem. Abstr.*, **32**, 4943 (1938).

time of 2 hr the reaction flask was placed in a 50° bath and the acetyl fluoride was distilled away from acetone using a tall, unpacked Teflon fractionating column to yield 11 g of high-purity, water-white acetyl fluoride identical in every respect with an authentic sample, and free of acetone as evidenced by in frared spectrum. Hydrofluoric acid was absent. The distillate gave no turbidity on mixing with carbon disulfide and could be stored in glass vessels.

Azelaoyl Fluoride.—A stream of hydrogen fluoride was bubbled through 45 g of diisopropenyl azelate[11] at 85° for 1.25 hr in Teflon apparatus. Only a slight darkening of color was noticeable. The ir spectrum showed no residual enol ester absorption bands but acetone absorption bands were evident. The analytical sample (yield 63%) was obtained by distillation: bp 80° (0.01 Torr); ir (CS_2) 1820 (C=O), 1075 cm^{-1} (CF).

Anal. Calcd for $C_9H_{14}O_2F_2$: C, 53.32; H, 7.83; F, 21.09. Found: C, 53.11; H, 7.80; F, 20.93.

(11) E. S. Rothman, S. Serota, and D. Swern, *J. Org. Chem.*, **31**, 629 (1966).

General Procedure for Stearoylation with Isopropenyl Stearate.—To 1 equiv of isopropenyl stearate at the indicated reaction temperature 1 equiv of the substance to be acylated was added followed by a catalytic amount of sulfuric acid (2 drops/10 g of isopropenyl ester). After the mixture was heated the indicated length of time, the product was isolated either by directly crystallizing, or by chromatography on Florisil (see Table I above).

Registry No.—Stearoyl fluoride, 1511-79-1; isopropenyl octanoate, 19886-81-8; azelaoyl fluoride, 13022-57-6; N-phenyl-N-stearoyl-*p*-toluenesulfonamide 19886-83-0; N-benzyl-N-stearoyl-*p*-toluenesulfonamide, 19886-84-1; N,N′-distearoylsulfanilamide, 19922-50-0; benzyl N-phenyl-N-stearoylcarbamate, 19886-85-2; phenyl N-phenyl-N-stearoylcarbamate, 19886-86-3.

Tools

August, 1969:

Additions, some intriguing, some merely reliable

Tool for epoxidation (but exceptionally stable itself)

m-Chloroperbenzoic Acid
(EASTMAN P10824)

Industrial product of 85% assay. Has attracted so much scientific interest that its producer has asked us to supply that demand. Converts olefins to epoxides, including volatile epoxides. Permits inversion of the carboxy reaction, with an acid becoming an alcohol. Eliminates difficulties in epoxidizing 7,8- and 8,9-unsaturated tetracyclic triterpenes. Converts cytosine and cytidine into the corresponding 3-N-oxides, where pertrifluoroacetic acid fails. Cleaves tetrahydrochromane to an interesting cyclic ketolactone. Seems to belong at every steroid chemist's right hand. Outperforms perphthalic acid or unsubstituted perbenzoic acid for stereoselectivity in preparation of cholesterol α-epoxide. Will oxidize a 20-ketosteroid, which by hydrolysis then goes to the 17β-hydroxysteroid. Turns steroid amines into nitrosteroids. See references in Fieser & Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, 1967, p. 135.

Tool for introducing azo groups

p-Toluenesulfonyl Azide
(EASTMAN 10871)
Also known as tosyl azide

With a basic catalyst, converts β-diketones to α-diazo-β-diketones [*Ann.*, *676*:101 (1964)]. In presence of piperidine converts anthrone to 9-diazoanthrone, which, on gentle warming in mixture of piperidine and pyridine, yields anthraquinoneazine [*Ber.*, *97*: 2742 (1964)]. Yields the remarkably stable, dark-red diazocyclopentadiene by reacting with cyclopentadienyllithium [*J.A.C.S.*, *75*:5955 (1953)]. Analogous reaction occurs with the more reactive phenols to result in diazooxides [*J. Chem. Soc.*, 4417 (1960)].

Tool for wide-scale adjustment of polarity in aqueous solutions

2,6-Lutidine (Spectro Grade)
(EASTMAN S4820)

The 37th of the EASTMAN Spectro Solvents, all furnished with firm data on IR windows. UV cutoff at 303 nm. Aside from spectrophotometry, this great solubilizer is also found useful in our own laboratories as a chromatographic eluent.

Tools for measuring conformational changes in proteins

8-p-Toluidino-1-naphthalenesulfonic Acid
(EASTMAN 10591)
Also known as 1,8-TNS

6-p-Toluidino-2-naphthalenesulfonic Acid
(EASTMAN 10613)
Also known as 2,6-TNS

Fluorescent probes which, on binding themselves to proteins, change in such fluorescent properties as quantum yield in response to denaturation or activation from a zymogen form. They do not fluoresce in water but turn on strongly when bound. [*Accounts of Chemical Research*, *1*:65 (1968)].

Tool for non-aqueous atomic absorption work

Mercury Cyclohexanebutyrate
(EASTMAN 10404)

Joins our 26 other organometallic standards. Each bottle supplied with a lot analysis, and data sheet describing the preparation of standard solutions.

Tool to protect the carboxyl group of an N-protected amino acid or peptide

N-Chloromethylphthalimide
(EASTMAN 10860)

Then the N-protecting carbobenzoxy groups can be safely removed by hydrogenation. The carboxy-protecting phthalimidomethyl is itself knocked off by 16-hour treatment with HCl in dioxane or ethyl acetate, by treatment with HBr in acetic acid for 10-15 minutes, or by 3-hour treatment with hydrazine hydrate in ethanol [Fieser & Fieser, p. 135].

Tool in protein synthesis for making activated water-soluble amino acid esters

N-Hydroxysuccinimide
(EASTMAN 9286)

Its water-soluble esters can also be prepared in organic solvent [*J.A.C.S.*, *86*: 1839 (1964)].

Eastman laboratory chemicals and EASTMAN CHROMAGRAM® products for thin-layer chromatography can be ordered from leading laboratory suppliers.