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Notice to Authors appears in this issue

EDITORIAL

Microfilm Edition and "Supplementary Data."—*The Journal of Organic Chemistry* appears both in printed form and in a microfilm edition. To date the microfilm edition has consisted solely of the material appearing in the printed version. Arrangements have been made to expand the microfilm edition by inclusion of various types of supplementary data that heretofore have only been avilable to the reader through direct contact with the author, through theses, or through the National Auxiliary Publications Service.

The new system will permit authors to present data such as key spectra or tables of experimental results that have not been handled in the printed journal. In addition to spectra and tables, authors may in some cases want to include expanded discussion of peripheral points which might otherwise be difficult to accommodate in the printed paper.

Supplementary material will be sent to reviewers for examination along with the full manuscript of a paper. The decision on what supplementary material to include in the microfilm edition will be made by the editor in consultation with the author. There is no charge to the author for supplemental pages in the microfilm edition.

The supplementary material will appear in the microfilm edition immediately following the article with which it is associated. A footnote in the printed journal will indicate the specific information in the microfilm supplement. Single copies of the supplementary material can be obtained on microfiche or printed form from the Reprint Department of the ACS Publications Office shortly after the journal issue appears. The supplementary data will be indexed by *Chemical Abstracts*.

X-Ray Data.—*The Journal of Organic Chemistry* receives increasing numbers of papers containing the results of X-ray crystallographic analysis. We are glad to consider the publication of crystallographic results for cases which we feel are of interest to organic or bioorganic chemists. However, we feel it is appropriate for this journal to publish only the final results of the X-ray analysis. This should include (1) unit cell parameters and standard errors, (2) the formula, formula weight, and number of formula units in the unit cell, (3) measured and calculated densities, (4) space group, (5) method of collection of intensity data, (6) number of reflections observed and (for diffractometer data) number of unobservedly weak reflections, (7) indication of the methods of structure solution and refinement, (8) comment regarding any features on a final difference Fourier map, (9) final R value, (10) bond lengths and angles and their standard deviations. Publication of a stereoscopic view of the molecule is encouraged. The supporting data (F tables, tables of final atomic parameters, positional and thermal, and their standard deviations) should be submitted as supplementary data for the microfilm edition (see above).

Analytical Data.—Adequate evidence to establish purity should be reported for new compounds. In general, this should include combustion analytical data. When such data are collected in tables they will not, in general, be printed. The data should, however, be included for examination by reviewers and editors. A footnote to the table should state that "Satisfactory analytical data ($\pm 0.4\%$ for C, H, N, etc.) were reported for all new compounds listed in the table." Any exceptions to this should be specifically stated in the footnote. The tabular analytical data, the footnote, and any exceptions should appear in the original and all revisions of the manuscript in such form that the editor at time of acceptance of a paper may verify and initial the footnote, and cross out the tabular analytical data. Isolated analyses should be reported in the Experimental Section in the usual format and will be printed.

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FREDERICK D. GREENE, EDITOR

THE JOURNAL OF Organic Chemistry®

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AUTHOR INDEX

In papers with more than one author the name of the author to whom inquiries about the paper should be addressed is marked with an asterisk in the by-line.

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Papers in which the primary interest lies in the implications of new compounds for medicinal, polymer, agricultural, or analytical chemistry are generally considered to be published most appropriately in specialized journals, together with information on evaluation with respect to the original reason for synthesis.

Manuscripts may be classified as "articles" or "notes." **Articles** should be comprehensive and critical accounts of work in a given area. **Notes** should be concise accounts of studies of a limited scope. The standards of quality for notes are the same as those for articles. Improved procedures of wide applicability or interest, or accounts of novel observations or of compounds of special interest, often constitute useful notes. Notes should not be used to report inconclusive or routine results or small fragments of a larger body of work but, rather, work of a terminal nature.

In particular, this journal encourages the submission of work as full accounts in the form of articles. Presentation of results in smaller papers or notes leads to undesirable fragmentation, especially in the case of continuing studies, and is contrary to the journal policy. When several closely related manuscripts are in preparation at about the same time, these should be submitted simultaneously. This procedure permits editors and reviewers to examine the manuscripts in an overall context and avoids the possibility of fragmentation of the work. If additional papers in a series are projected, notification of the editors to this effect, with an approximate timetable, is advisable and will be appreciated.

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Republication of Preliminary Communication.—It is understood that contributions submitted to the journal will not previously have been published elsewhere, and are based upon original results. Articles based upon work previously reported as a brief preliminary communication will be considered provided that they represent a *substantial amplification* and, generally, an extension of the earlier communication. Extensive recapitulation of previously published results or experimental data should be avoided.

If significant data or conclusions in a manuscript have been published previously in preliminary form, reference to the earlier publication must be given. Three reprints or other copies of the preliminary communication are needed for use by the editors and reviewers; to avoid delays, these should be submitted with the manuscript.

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All manuscripts *including notes* must be accompanied by an abstract. The abstracts, in general, are used directly in *Chemical Abstracts* (CA indexes are prepared from the full paper). The abstracts for notes will not be printed in *The Journal of Organic Chemistry;* they should be submitted on a separate sheet for direct transmittal to *Chemical Abstracts* by this journal.

An abstract should state briefly the purpose of the research (if this is not contained in the title), the principal results, and major conclusions. Reference to structural formulas or tables in the text, by number, may be made in the abstract. For a typical paper, an 80–200-word abstract is usually adequate.

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The discussion and experimental sections should be clearly distinguished, with a separate center heading for the latter; other center headings should be used sparingly. The presentation of experimental details in the discussion section, *e.g.*, physical properties of compounds, should be kept to a minimum.

All sections of the paper must be presented in as concise a manner as possible consistent with clarity of expression. In the Experimental Section, specific representative procedures should be given when possible, rather than repetitive individual descriptions. Standard techniques and procedures used throughout the work should be stated at the beginning of the Experimental Section. Tabulation of experimental results is encouraged when this leads to more effective presentation or more economical use of space. Spectral data should be included with other physical properties and analyses of compounds in the Experimental Section or in tables. Separate tabulations of spectral values should be used only when necessary for comparisons and discussion.

In lengthy papers, authors are encouraged to organize the manuscript so that the principal findings and conclusions are concisely presented in an initial section (Part A), with supporting data, experimental details, and supplementary discussion in a Part B [see *J. Org. Chem.*, **35** (11), 16A, 3591–3646 (1970)].

Spectra.—Reproductions of spectra, or the relevant segments thereof, will be published only if concise numerical summaries are inadequate for the purposes of the paper. Papers dealing primarily with interpretation of spectra, and those in which band shape or fine structure needs to be illustrated, may be published with such spectra included. When presentation of spectra is deemed essential, only the pertinent sections (prepared as indicated for "Illustrations") should be reproduced. Spectra will not be published merely as adjuncts to the characterization of compounds. However, spectra may be submitted for publication in the microfilm edition (see below). Routine spectral data should be summarized in the Experimental Section (see below).

Microfilm Edition and Supplementary Data.—Arrangements have been made to expand the microfilm edition of this journal to include various types of "supplementary" data (*e.g.*, spectral data, X-ray data, expanded discussion of peripheral points, etc.). A footnote in the paper [for format, see *J. Org. Chem.*, **36,** 2 (1971), footnote 2] will indicate the nature of the supplementary data to be found in the microfilm edition. For the microfilm edition, captions or legends for figures, spectra, etc., should appear *directly on the figure* rather than on a separate page as required for the printed edition. Single copies of the supplementary material can be obtained from the Reprint Department of the ACS Publications Office. For further information, see Editorial, *J. Org. Chem.*, **36** (13), 2A (1971).

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Footnotes include both literature citations and explanatory notes and must, therefore, be numbered in one consecutive series. In the text, footnotes are indicated as unparenthesized superscripts. The footnotes may be placed, suitably offset, following the line of text in which they are cited, or they may be grouped in numerical order at the end of the manuscript. All nontechnical information (grant numbers, present address of author to whom inquiries should be directed if this information is not obvious from the heading, etc.) should be given in the subdivisions (a, b, c, . . .) of footnote 1. Addresses of coauthors should not be included. An asterisk designates the name of the author to whom correspondence should be sent.

In literature references, journal abbreviations should be those used by *Chemical Abstracts* (see *Chemical Abstracts Service Source Index*, formerly *Access*).

Tables should be numbered consecutively with Roman numerals and should be included at the proper places in the manuscript. Footnotes in tables should be given letter designations and cited in the table by superscript letters. The sequence of letters should proceed by line rather than by column. If a footnote is cited both in the text and in a table, insert a lettered footnote in the table to refer to the numbered footnote in the text. Each table should be provided with a descriptive heading, which, together with the individual column headings, should make the table, as nearly as possible, self-explanatory. In setting up tabulations, authors are requested to keep in mind the type area of the journal page (7 × 10 in.), and the column width (approximately $3^1/_4$ in.), and to make tables conform to the limitations of these dimensions. Arrangements that leave many columns partially filled or that contain much blank space should be avoided insofar as possible.

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Although fairly complicated structures can be redrawn in the standard format, unusually complex formulas, or drawings in which perspective is crucial, may be better submitted as copy suitable for direct photographic preparation of an engraving. It is *not* necessary to provide such copy for standard structural formula layouts. In the preparation of engraver's copy of complex drawings, careful lettering (*e.g.*, with a Leroy set or similar device) is required.

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Standard **abbreviations** should be used throughout the Experimental Section. *Please note that these are used in ACS journals* **without** *periods.* The preferred forms for a few of the more commonly used abbreviations are mp, bp, min, hr, μl, ml, g, mg, cm, Hz, nm, ppm, tlc, vpc (or gc), nmr, uv, and ir. The abbreviation for liter, l., has a period to distinguish it from the numeral "one."

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Physical constants and spectral data should be presented in a uniform way as illustrated in the following example.

(In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet.)

"The ethereal extract was dried ($MgSO_4$), concentrated, and distilled giving 10.23 g (65%) of the acetoxy ketone **12**: bp 82–83° (2.9 mm); n_D^{25} 1.4266 [lit.[6] bp 80–82° (3 mm); n_D^{25} 1.4261]; d_4^{25} 0.823; $[\alpha]_D^{25}$ 0.0° (*c* 6, CH_3OH); uv max (95% EtOH) 275 nm (ε 21); ir (CCl_4) 1725 (C=O), 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 3.98 (t, 2, *J* = 6 Hz, CH_2OAc), 2.43 (t, 2, *J* = 6 Hz, CH_2CO), 2.07 (s, 3), 1.97 (s, 3), and 1.6 (m, 4); mass spectrum (70 eV) *m/e* (rel intensity) 158 (5), 143 (5), 115 (6), 100 (50), 99 (11), 98 (100), 85 (10)."

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JULY 2, 1971

Adducts of Sulfonyl Iodides with Acetylenes[1]

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Received November 10, 1970

Sulfonyl iodides, including three previously unknown alkane derivatives, add readily and stereoselectively to acetylenes to form 1:1 adducts in good to excellent yields. That the addition occurs in a trans manner was established by reducing the adducts to the *cis*-vinyl sulfones with zinc and acetic acid and by three-dimensional X-ray crystallography. The adducts represent convenient precursors to sulfonylacetylenes and, on treatment with cuprous phenylacetylide, yield the novel ene–yne sulfones. The acetylenic sulfones undergo a smooth thermally induced extrusion of sulfur dioxide in several cases.

Free-radical additions of sulfonyl halides to olefins have been studied extensively. Thus, Kharasch, *et al.*, initially found that *N*-chlorosulfonylphthalimide and 1-octene combined, in the presence of traces of peroxide, to give a 1:1 adduct.[2] Cristol and coworkers[3] studied the reactions between benzenesulfonyl halides (chloride, bromide, and iodide) and norbornadiene, and Skell, *et al.*,[4,5] carried out extensive synthetic investigations and rate studies with the same three sulfonyl halides. For addition to olefins, the chain mechanism as shown in Scheme I is generally accepted.

SCHEME I

$$C_6H_5SO_2X \longrightarrow C_6H_5SO_2\cdot + X\cdot \quad (1)$$

$$C_6H_5SO_2X + In\cdot \longrightarrow C_6H_5SO_2\cdot + InX \quad (2)$$

$$C_6H_5SO_2\cdot + RCH{=}CH_2 \longrightarrow RCHCH_2SO_2C_6H_5 \quad (3)$$

$$RCHCH_2SO_2C_6H_5 + C_6H_5SO_2X \longrightarrow RCH(X)CH_2SO_2C_6H_5 + C_6H_5SO_2\cdot \quad (4)$$

Steps 1 and 2 are the initiating steps (where In· represents an added initiator such as peroxide) and steps 3 and 4 are the propagating steps. Although all three sulfonyl halides undergo the above sequence, there is a marked difference in the rate at which each proceeds. Thus, benzenesulfonyl chloride combines with norbornadiene very slowly (giving a 7.3% combined yield of 1:1 adducts after 56 hr near a 150-W clear electric bulb), while the sulfonyl bromide adds smoothly (90% after 27 hr near illumination) and the iodide and the diene combine in a violent, exothermic manner.[3]

Although sulfonyl halide additions to olefins have received considerable attention[2-9] and constitute a valuable synthetic approach to various sulfones, like additions to other unsaturated systems seem to have been neglected. Amiel[10] stated that aromatic sulfonyl chlorides add to acetylenes to give 1:1 adducts, but no experimental details have been forthcoming. Also, a preliminary report of our investigations, concerning the additions of sulfonyl iodides to allenes,[11,12] has appeared.

p-Toluenesulfonyl iodide has been found to add readily and stereoselectively to numerous acetylenes. The

$$p\text{-}CH_3C_6H_4SO_2I + RC{\equiv}CR' \longrightarrow \underset{\mathbf{3}}{\overset{R}{\underset{I}{\diagdown}}\!\!>C{=}C<\!\!\overset{p\text{-}SO_2C_6H_4CH_3}{\underset{R'}{\diagup}}}$$

ease with which the reactions were carried out is worthy of note. Equivalent quantities of the iodide and the desired acetylene were dissolved in ether or benzene. Anhydrous conditions were initially used, but it was later found that scrupulous drying of solvents and reagents was not necessary. On exposure to illumina-

(1) Abstracted from the Ph.D. Thesis of G. C. W., Purdue University, 1970.

(2) (a) M. S. Kharasch and A. F. Zaviet, *J. Amer. Chem. Soc.*, **73**, 964 (1951); (b) M. S. Kharasch and R. A. Mosher, *J. Org. Chem.*, **17**, 453 (1952).

(3) (a) S. J. Cristol and J. A. Reeder, *ibid.*, **26**, 2182 (1962); (b) S. J. Cristol and D. I. Davies, *ibid.*, **29**, 1282 (1964).

(4) (a) P. S. Skell and J. H. McNamara, *J. Amer. Chem. Soc.*, **79**, 85 (1957); (b) P. Skell, R. C. Woodworth, and J. H. McNamara, *ibid.*, **79**, 1253 (1957).

(5) J. H. McNamara, Ph.D. Thesis, The Pennsylvania State University, 1956.

(6) C. M. M. da Silva Correa and W. A. Waters, *J. Chem. Soc. C*, 1874, 1880 (1969).

(7) C. T. Goralski, Ph.D. Thesis, Purdue University, 1969.

(8) M. Assher, *Chem. Ind. (London)*, 32 (1964).

(9) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 4962 (1964).

(10) Y. Amiel, Abstracts of Papers, Second Organic Sulfur Symposium, Groningen, The Netherlands, 1966.

(11) W. E. Truce and G. C. Wolf, *Chem. Commun.*, 150 (1969).

(12) Whereas allene yields *p*-$CH_2{=}CClCH_2SO_2C_6H_4CH_3$, phenylallene yields $C_6H_5CH{=}C(p\text{-}SO_2C_6H_4CH_3)CH_2I$.

TABLE I

ADDUCTS OF *p*-TOLUENESULFONYL IODIDE WITH ACETYLENES

Product	Acetylene	Yield, %	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	I, % Calcd	I, % Found	S, % Calcd	S, % Found
3a	$C_6H_5C{\equiv}CH$	87	83–84	46.89	46.72	3.41	3.55	33.03	32.83	8.34	8.50
3b	$c\text{-}C_6H_{11}C{\equiv}CH$	74	108.5–109.5	46.16	46.28	4.91	5.16	32.52	32.62	8.22	7.99
3c	$C_6H_5C(O)C{\equiv}CH$	83	155–156	46.62	46.56	3.18	3.25	30.78	30.90	7.78	8.00
3d	$C_2H_5O_2CC{\equiv}CH$	32	98–99	37.91	38.12	3.45	3.65	33.38	33.55	8.43	8.72
3e	$NCC{\equiv}CH$	16	123–124	36.05	35.92	2.42	2.22	38.09	37.90	9.62	9.82
3f	$p\text{-}NO_2C_6H_4C{\equiv}CH$	68	203–204	41.97	42.25	2.82	2.93	29.56	29.27	7.47	7.76
3g	$n\text{-}C_4H_9C{\equiv}CH$	82	50.0–50.5	42.87	42.87	4.70	4.59	34.84	34.58	8.80	8.80
3h	$p\text{-}CH_3C_6H_4SC{\equiv}CH$	80	135–136	44.66	44.37	3.51	3.55	29.49	29.69	14.90	14.89
3i	$(CH_3)_2CHC{\equiv}CH$	69	71–72	41.15	41.23	4.32	4.37	36.24	35.99	9.16	9.23
3j	$n\text{-}C_6H_{13}C{\equiv}CH$	74	55–56	45.93	45.74	5.40	5.51	32.35	32.35	8.17	8.17
3k	$(CH_3)_3CC{\equiv}CH$	86	70–105[a]	42.87	42.90	4.70	4.89	34.84	34.90	8.80	8.90
3l	$C_6H_5C{\equiv}CC_6H_5$	35	192–193	54.79	54.53	3.72	3.91	27.57	27.57	6.97	6.75
3m	$C_6H_5C{\equiv}CCl$	79	146–147	43.03	43.03	2.89	3.00	30.31	30.01	7.66	7.49
3n	$C_2H_5C{\equiv}CC_2H_5$	84	66–67	42.87	42.63	4.70	4.84	34.84	34.84	8.80	9.03

[a] This is the only instance where both isomers were observed; the analysis was obtained on the mixture.

TABLE II

ADDITION OF ALKANESULFONYL IODIDES TO ACETYLENES

Product	Acetylene	Iodide	Yield, %	Mp, °C [bp (mm), °C]	C, % Calcd	C, % Found	H, % Calcd	H, % Found	I, % Calcd	I, % Found	S, % Calcd	S, % Found
4a	$C_6H_5C{\equiv}CH$	CH_3SO_2I	73	84–85, 94–95[a]	35.08	34.87	2.94	3.20				
4b	$C_2H_5C{\equiv}CC_2H_5$	CH_3SO_2I	24	54–55	29.18	29.46	4.55	4.57				
5a	$C_6H_5C{\equiv}CH$	$C_2H_5SO_2I$	80	77–78	37.28	37.45	3.44	3.34				
5b	$n\text{-}C_4H_9C{\equiv}CH$	$C_2H_5SO_2I$	44	[120–124 (0.01)]	31.80	31.97	5.00	5.15				
6	$C_6H_5CC{\equiv}CH$	$i\text{-}C_3H_7SO_2I$	53	130–131	39.30	39.59	3.89	3.84	37.75	37.50	9.54	9.50
7	$C_6H_5CC{\equiv}CH$	$tert\text{-}C_4H_9SO_2I$	15	213–214	41.15	41.43	4.32	4.26	36.24	36.00	9.16	9.00

[a] Two interconvertible crystalline forms were obtained.

tion,[13] the yellow solution usually began to lighten after 5–20 min (in some cases, the solution darkened instead, and, when this occurred, the yield of adduct was generally less). Solvent removal gave the product as a solid residue and, after one recrystallization from ethanol–water, the essentially pure *trans*-β-iodovinyl sulfone was obtained (Table I). Although electron-withdrawing substituents on the triple bond seem to lower the yield of adduct in some cases (*i.e.*, **3d** and **3e**), in other instances there is little apparent effect (**3c**, **3f**, **3m**). Furthermore, internal acetylenes (**3m**, **3n**) react in a comparable fashion to terminal ones. (Note, however, the lowered yield of adduct when tolane was the substrate.) All products in Table I were obtained as crystalline solids; however, their stability varied. Whereas most were seemingly unchanged after 1 year in the dark, **3h** decomposed quite rapidly. When exposed to the atmosphere and incident light for as little as 24 hr, the adduct began to decompose noticeably; after 1 week, it was quite dark and iodine vapors were apparent above the solid.

With the encouraging results obtained above, the scope of the reaction was extended to include other sulfonyl iodides. The only alkanesulfonyl iodide described in the literature to date is the methyl derivative.[14] Methanesulfonyl iodide was prepared as intense green needles which defied our attempts at purification. It could not be dried under vacuum without decomposition nor did we find a suitable solvent system to effect recrystallization. Hence, it was initially used as the impure, wet solid. However, though a 1:1 adduct was obtained with phenylacetylene when this solid was used, 1,2-diiodostyrene was also formed in large quantities. For this reason, as well as for convenience, methanesulfonyl iodide was prepared and used *in situ* by mixing an aqueous solution of sodium methanesulfinate with a benzene solution of iodine. In the same manner, ethane-, 2-propane-, and *tert*-butanesulfonyl iodides were prepared. The yields were generally lower than with *p*-toluenesulfonyl iodide, but perhaps more noteworthy is the fact that the adducts could be prepared at all. Thus, at the end of the reaction period, the biting odor of sulfur dioxide was evident above each solution; presumably the intermediate alkanesulfonyl radical was extruding sulfur dioxide.

$$RSO_2I \longrightarrow I\cdot + RSO_2\cdot \longrightarrow R\cdot + SO_2$$

Indeed, van Aller, *et al.*,[15] have reported that *tert*-butanesulfonyl chloride is unstable and decomposes to *tert*-butyl chloride, isobutylene, sulfur dioxide, and hydrogen chloride with a half-life of 34 hr at 35°. The iodide would be expected to be less stable.

As noted in Table I, only in the *p*-toluenesulfonyl iodide–*tert*-butylacetylene reaction were two isomeric products found. The adducts listed in Table II were also obtained as a single pure isomer in each case. To eliminate the possibility that a second isomer was being lost during purification procedures, several of the crude reaction mixtures were analyzed by nmr spectroscopy before work-up. For example, in the preparation of **3i**, after the normal reaction period, the volatile materials were removed at reduced pressure and a bath temperature not exceeding 45°. An nmr spectrum of

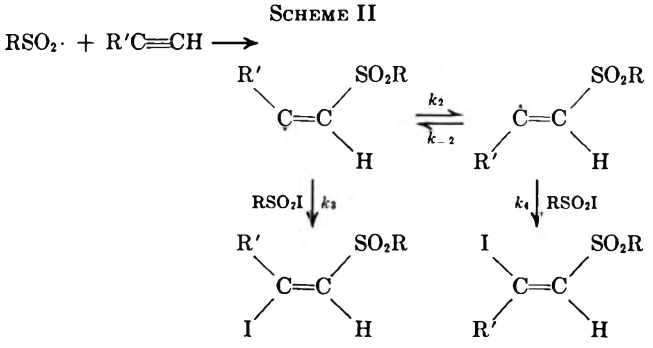
(13) For the reactions discussed here, a 250-W General Electric heat lamp was employed; however, the additions could also be effected by the influence of a 200-W Hanovia medium-pressure lamp (using a Pyrex filter). Indeed, the reactions proceeded in the dark but were markedly catalyzed by light. Thus, after 132 min in the dark, the reaction between 1-hexyne and *p*-toluenesulfonyl iodide had proceeded to 29% completion; after an additional 15 min near the heat lamp, the reaction was 70% complete (by nmr).

(14) L. Field, T. F. Parsons, and R. R. Crenshaw, *J. Org. Chem.*, **29**, 918 (1964).

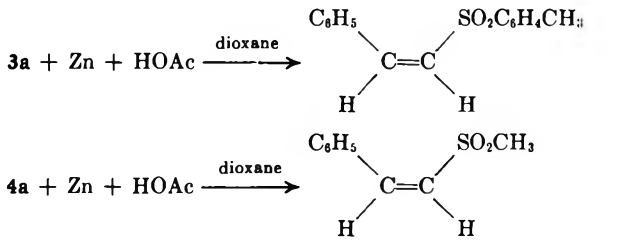
(15) R. T. van Aller, R. B. Scott, Jr., and E. L. Brockelbank, *ibid.*, **31**, 2357 (1966).

the residue showed only one vinyl proton peak and only one set of isopropyl protons. Analogous results were obtained for several other reactions. Furthermore, the reaction between *p*-toluenesulfonyl iodide and 1-hexyne was followed from 0 to 75% completion by periodically withdrawing samples, removing the solvent, and analyzing the residue by nmr. Again, throughout the course of the reaction, only one vinyl proton and one vinyl methylene group could be detected. This remarkable stereoselectivity parallels that reported by Cristol, *et al.*[3] It would appear that chain transfer by the sulfonyl iodide (k_3) is much faster than isomerization of the intermediate vinyl radical (k_2) (Scheme II).[16]

SCHEME II

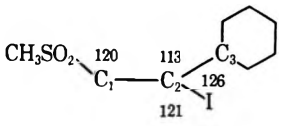


That the sulfonyl iodides were, indeed, adding in a trans fashion was established by two methods. Thus, **3a**, **3b**, and **4a** were reduced with zinc and acetic acid



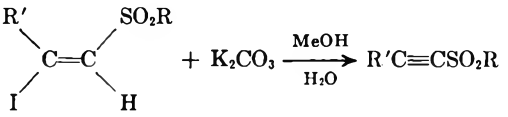
to give only the *cis*-vinyl sulfone. No trans product could be detected by nmr in the crude reaction mixture.

A more unambiguous structural proof was sought, and to this end an X-ray crystallographic analysis was performed on one of the adducts.[17] Crystals of the adduct from methanesulfonyl iodide and phenylacetylene were found to belong to the C2/C monoclinic space group and yielded 2400 good intensities. The cell dimensions were a = 12.393 Å, b = 10.463 Å, c = 17.220 Å, and β = 101.91°. The results of this study confirm our chemical evidence. A more detailed account will be reported later, but these preliminary results (with an R value = 0.17) unequivocally show that the iodine and sulfur atoms are located trans to



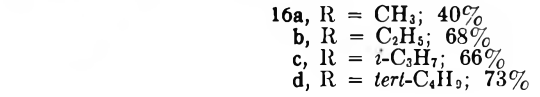
each other. The pertinent bond angles are shown in structure a. The atoms S, C_1, C_2, C_3, and I very nearly lie in the same plane. There is a possible twist of less than 10° about the carbon–carbon double bond. Interestingly, the plane of the benzene ring is close to perpendicular to that described by S, C_1, C_2, C_3, and I.

As β-bromo vinyl ketones can be dehydrohalogenated to the acetylenic ketones *via* treatment with potassium carbonate in methanol–water,[18] so can these adducts (Table III). Attempts to dehydroiodinate **3c**, **3f**, and



3h met with only limited success. The crude products in each case showed a band at *ca.* 4.5 μ in the ir spectrum, but the pure acetylenic sulfone could not be isolated. In all three cases, spectral evidence indicated the presence of varying amounts of the products resulting from methoxide and hydroxide displacement on the vinyl iodide.

Compounds **12**–**15** smoothly extrude sulfur dioxide to yield the disubstituted acetylenes on heating, *i.e.*,



Though thermal rearrangements of organic sulfur compounds have been reported (*i.e.*, α disulfones,[19] α-sulfinyl sulfones,[20] and allylic sulfones[21]), as far as we are aware, this is the first report of acetylenic sulfones behaving likewise. The present rearrangement is limited in scope, however. For the reaction to proceed significantly, R in **16** must be an alkyl group; and also, the substituent on the acetylenic carbon must be aryl. When R = C_6H_5, the pyrolysis gave large quantities of sulfur dioxide but none of the hoped-for tolane. Further, no 3-octyne was obtained when 1-ethanesulfonyl-1-hexyne was heated to 300°, although sulfur dioxide was again evolved. Finally, only starting material (no sulfur dioxide) was recovered when 1-*p*-toluenesulfonyl-1-octyne was heated to 280°.

Copper acetylides have recently been shown to be

(16) Vinyl radicals have recently received much attention regarding their structure and configuration. Several reports have appeared dealing with the additions of various radicals to terminal acetylenes. Such addends include chloroform thiolacetic acid, tetrafluorohydrazine, organic disulfides, and thiols. In every case but one (tetrafluorohydrazine), the predominate product was that resulting from trans addition of the attacking reagent. The current work is unique in that only one isomer was detected in all the additions studied (save that employing *tert*-butylacetylene). This suggests that sulfonyl iodides are much better chain transfer agents than any of the above-mentioned addends. Moreover, we have found that in the cupric bromide catalyzed addition of benzenesulfonyl bromide to phenylacetylene there can be isolated two isomeric α-bromo-β-(benzenesulfonyl)-styrenes. This result serves to enforce the work of Skell and McNamara who found that, in the additions to norbornadiene, benzenesulfonyl bromide and chloride both led to much greater amounts of internally rearranged products than did benzenesulfonyl iodide. For leading references in this area of vinyl radicals and radical additions to terminal acetylenes, see J. A. Kampmeier and G. Chen, *J. Amer. Chem. Soc.*, **87**, 2608 (1965); R. M. Fantazier and J. A. Kampmeier, *ibid.*, **88**, 5219 (1966); R. M. Kopchik and J. A. Kampmeier, *ibid.*, **90**, 6733 (1968); G. N. Sausen and A. L. Logothetis, *J. Org. Chem.*, **32**, 2261 (1967); E. I. Heiba and R. M. Dessau, *ibid.*, **32**, 3837 (1967); L. A. Singer and J. Chen, *Tetrahedron Lett.*, 4849 (1969).

(17) The authors express their sincere gratitude to Dr. R. Parthasarathy of the Center of Crystallographic Research, Roswell Park Division of Health Research, Inc., Buffalo, N. Y., for carrying out the difficult and time-consuming analysis.

(18) P. Eaton and C. Stubbs, *J. Amer. Chem. Soc.*, **89**, 5722 (1967).

(19) J. L. Kice and N. A. Favstritsky, *J. Org. Chem.*, **35**, 114 (1970).

(20) J. L. Kice and N. E. Pawlowski, *J. Amer. Chem. Soc.*, **86**, 4898 (1964).

(21) E. M. LaCombe and B. Stewart, *ibid.*, **83**, 3457 (1961).

TABLE III
ACETYLENIC SULFONES

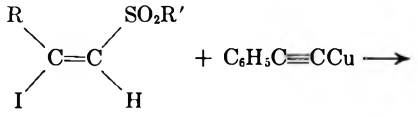
Compd	Formula	Yield, %	Mp, °C [bp (mm), °C]	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S, % Calcd	S, % Found
8	p-$C_6H_5C{\equiv}CSO_2C_6H_4CH_3$	86	83–84						
9	p-$(CH_3)_3CC{\equiv}CSO_2C_6H_4CH_3$	100	99.5–100.5	66.08	66.07	6.83	6.70	13.55	13.58
10	p-$(CH_3)_2CHC{\equiv}CSO_2C_6H_4CH_3$	61	44–45	64.83	65.18	6.35	6.45	14.42	14.34
11	n-$C_4H_9C{\equiv}CSO_2C_2H_5$	31	[124–126 (1.3)]	55.14	54.88	8.09	8.08	18.40	18.28
12	$C_6H_5C{\equiv}CSO_2CH_3$	88	63–64	59.98	60.09	4.47	4.57	17.79	17.81
13	$C_6H_5C{\equiv}CSO_2C_2H_5$	*a*	*a*	61.83	61.31	5.19	4.96	16.51	16.08
14	$C_6H_5C{\equiv}CSO_2CH(CH_3)_2$	52	*a*	63.43	63.56	5.81	5.94		
15	$C_6H_5C{\equiv}CSO_2C(CH_3)_3$	72	66–67	64.83	64.78	6.35	6.38	14.42	14.30

[a] The product was purified by elution chromatography; these two acetylenes were viscous oils and could not be purified by vpc or distilled because of decomposition.

valuable intermediates in organic synthesis.[22-24] To date, most of this work has dealt with the displacement of aryl iodides by the acetylides. Only one instance of attack on vinyl halides has been reported. Burdon, *et al.*,[25] have briefly described the reaction between various copper acetylides and simple iodoethylenes.

$$CHI{=}CHCl + C_6H_5C{\equiv}CCu \xrightarrow{\text{pyridine}} \underset{90\%}{C_6H_5C{\equiv}CCH{=}CHCl}$$

We have found that copper phenylacetylide reacts with our 1:1 adducts to yield the novel ene–yne sulfones.



$$+ C_6H_5C{\equiv}CCu \longrightarrow C_6H_5C{\equiv}CC(R){=}CHSO_2R'$$

17a, R = c-C_6H_{11}; R′ = p-$CH_3C_6H_4$; 80%
b, R = C_6H_5; R′ = C_2H_5; 56%
c, R = C_6H_5; R′ = p-$CH_3C_6H_4$; 15%

Whether the stereochemistry about the double bond was retained during the reaction has not yet been determined.

Experimental Section[26]

Materials.—Phenylacetylene, cyclohexylacetylene, ethylpropiolate, and diphenylacetylene were purchased from Aldrich Chemical Co. and were used without further purification. 1-Hexyne, 3-hexyne, 3-methyl-1-butyne, 3,3-dimethyl-1-butyne, and 1-octyne were obtained from Farchan Research Laboratories. Phenyl ethynyl ketone was prepared by the method of Bowden, *et al.*;[27] p-nitrophenylacetylene was also prepared according to the literature[28] as were p-toluenethioacetylene[29] and phenyl chloroacetylene.[30] The sulfonyl iodides were prepared from the sodium sulfinates and molecular iodine. The alkanesulfinates were prepared from the corresponding sulfonyl chlorides by their reduction with sodium sulfite and sodium bicarbonate. Methane- and ethanesulfonyl chloride were purchased from Aldrich and Eastman, respectively. 2-Propanesulfonyl chloride had to be prepared from Eastman's sodium 2-propanesulfonate. Sodium *tert*-butanesulfinate was prepared from *tert*-butylmagnesium chloride and sulfur dioxide.[15] Sodium p-toluenesulfinate was purchased from Aldrich.

General Procedure for the Preparation and Additions of the Sulfonyl Iodides.—p-Toluenesulfonyl iodide[31] was prepared by adding an equivalent quantity of a concentrated ethanolic solution of iodine to a very dilute solution of sodium p-toluenesulfinate in water. The sulfonyl iodide precipitated out immediately as a flocculent, yellow solid. Recrystallization from carbon tetrachloride gave the product as bright yellow needles which began to decompose in a few hours, mp 90–95° dec (lit.[31] mp 90–91° dec). Consequently, it was prepared fresh each time that it was used. However, it was found that the solid was relatively stable if kept at −10 to 0° in carbon tetrachloride. For the acetylene additions, the sulfonyl iodide was used as the yellow solid which had been dried under vacuum for 1 hr.

The alkanesulfonyl iodides were prepared *in situ* from an aqueous solution of an excess of the sodium sulfinate and a benzene solution of iodine. On vigorous mixing of these two solutions, the intense purple color of the iodine faded and was replaced by the yellow-orange color of the sulfonyl iodide. The benzene layer was separated and dried briefly over anhydrous magnesium sulfate and filtered to give a clear, orange solution of the sulfonyl iodide. For the addition reaction, the desired acetylene was dissolved in a small amount of benzene and added to the iodide solution. Under the influence of a light,[13] the solutions (ether was the solvent used for the p-toluenesulfonyl iodide additions) were allowed to stir for 1–20 hr. Removal of the solvent under reduced pressure left the adduct. When feasible, the residue was recrystallized from ethanol–water. With the alkanesulfonyl iodides, the yields are based on the amount of iodine used. The following experiments illustrate the general procedure.

1-Iodo-1-cyclohexyl-2-p-toluenesulfonylstyrene (3a).—The sulfonyl iodide (13.02 g, 0.0462 mol) and cyclohexylacetylene (5.00 g, 0.0462 mol) were combined in *ca.* 200 ml of Mallinckrodt anhydrous ether. The resulting homogeneous yellow solution was stirred under illumination for 18 hr. The ether was removed at reduced pressure leaving a pale orange oil which solidified on standing. This solid was dissolved in hot 95% ethanol and water was added until the solution became faintly cloudy. After overnight refrigeration the 1:1 adduct was collected by filtration to give, after vacuum drying, 13.35 g (74%) of **3a** as white platelets, mp 108.5–109.5°.

1-Iodo-1-*tert*-butyl-2-p-toluenesulfonylethene (3k).—3,3-Dimethyl-1-butyne (2.46 g, 0.03 mol) and the iodide (8.46 g, 0.03 mol) afforded 9.44 g (86%) of **3k** (Table I). Analysis of this mixture by nmr showed it to consist of a 55:45 mixture of trans–cis adducts (trans refers to the adduct resulting from trans addition). The isomers were separated by adsorption chromatography using a silica gel column with benzene as the eluent. The trans adduct had mp 77–78°; the cis adduct melted at 136–137°. This same reaction was carried out two more times and in all three cases the trans:cis ratio was essentially the same.

α-Iodo-*cis*-β-methanesulfonylstyrene (4a).—The sulfonyl iodide, prepared according to the published procedure,[24] was obtained as intense, deep green needles. The needles were filtered from an aqueous solution and were wet; they could not be dried under vacuum as they readily decomposed. Hence, it was impossible to determine an accurate weight of the starting material

(22) C. E. Castro and R. S. Stephens, *J. Org. Chem.*, **28**, 2163, 3313 (1963).
(23) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *ibid.*, **31**, 4071 (1966).
(24) R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1097, 1108, 1117 (1964).
(25) J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *Chem. Commun.*, 1259 (1967).
(26) All melting points are uncorrected; microanalysis were performed by Dr. C. S. Yeh and staff of Purdue University.
(27) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(28) S. Cristol, A. Begoon, W. Norris, and P. Ramey, *J. Amer. Chem. Soc.*, **76**, 4558 (1954).
(29) W. E. Truce, H. E. Hill, and M. M. Boudakian, *ibid.*, **78**, 2760 (1956).
(30) R. Truchet, *Ann. Chim. (Paris)*, **16**, 309 (1931).
(31) F. C. Whitmore and N. Thurman, *J. Amer. Chem. Soc.*, **45**, 1068 (1923).

and, likewise, the "true" yield of addition product obtained was certainly higher than indicated.

The reaction between methanesulfonyl iodide (8.24 g, 0.04 mol) and phenylacetylene (4.60 g, 0.045 mol) was carried out in 200 ml of ether. (The sulfonyl iodide, when dissolved in ether, was so wet that several droplets of water formed in the bottom of the flask.) After 2 hr of stirring, the solution was washed with aqueous sodium thiosulfate and dried, and the solvent was removed under vacuum. The residue was dissolved in ethanol–water and cooled. By fractional crystallization two products were isolated. The less soluble (3.40 g) proved to be 1,2-diiodostyrene. The expected product was obtained by further cooling. There was collected 3.04 g (24%), mp 82–84°.

The same reaction was carried out a second time without isolating the wet methanesulfonyl iodide. Thus, sodium methanesulfinate (71.46 g, 0.70 mol) was dissolved in 200 ml of water and mixed with 1000 ml of a benzene solution containing 126.90 g (0.50 mol) of iodine. Separation and drying gave a solution which was more of a dark orange-brown color than the *p*-toluenesulfonyl iodide solution, but it was much lighter than the solid, green methanesulfonyl iodide. Phenylacetylene (61.28 g, 0.60 mol) in 500 ml of benzene was added and the mixture was stirred near a light for 2 hr, at which time the color was a light orange. Solvent removal left a residue which was dissolved in 900 ml of 95% ethanol. Decolorization with activated charcoal and filtration gave a clear yellow solution. On cooling, 99.57 g of a product in the form of white platelets was collected, mp 94–95°. Water was added to the mother liquor and, on further cooling, there was isolated 20.10 g of white needles, mp 73–85°. This second crop was recrystallized from ethanol–water to give 3.60 g of broad white needles which were identified as 1,2-diiodostyrene. Also obtained was 13.36 g of white needles, mp 84–85°. This product was identified as the sulfonyl iodide–acetylene adduct. The difference in melting points and crystalline forms of this product and that obtained initially was resolved on finding that the needles (mp 84–85°) could be dissolved in, and recrystallized from, ethanol–water to give the white platelets (mp 94–95°) and, conversely, the platelets could be recrystallized in the form of the lower melting needles. Hence, the methanesulfonyl iodide–phenylacetylene adduct could exist in either of two different crystalline forms. Total yield = 99.57 g + 13.36 g = 112.93 g (73%).

1-Iodo-2-ethyl-*cis*-1-ethyl-2-*p*-toluenesulfonylethene (4b).—Methanesulfonyl iodide (13.40 g, 0.065 mol, as a wet green solid[14]) and 3-hexyne (16.43 g, 0.20 mol) were combined in ether. After 2 hr the solvent was removed under reduced pressure to leave an oily residue. On attempted distillation, a red liquid was collected at bp 65–70° (0.05-mm pressure) to leave a dark pot residue. On standing, this residue solidified and was recrystallized from ethanol–water to give 4.50 g (24%) of **4b** (Table II).

General Procedure for Preparation of Acetylenic Sulfones.—The acetylene–sulfonyl iodide adducts were dissolved in sufficient methanol to effect solution. An equivalent quantity of potassium carbonate was dissolved in a minimum amount of water and added to the alcoholic solution. The mixture was heated slightly (40–70°) for 0.5–3 hr with stirring. The methanol–water solution was placed under reduced pressure and *ca.* $^2/_3$ of the solvent was removed. To the residue was added 200 ml of water. This mixture was extracted with ether or chloroform. Evaporation of the solvent left the crude product.

1-Phenyl-2-*p*-toluenesulfonylethyne (8).—**3a** (15.37 g, 0.04 mol) and potassium carbonate (5.53 g, 0.04 mol) afforded 8.83 g (86%) of **8** (Table III), mp 83–84° (lit.[32] mp 80–81°).

1-*tert*-Butyl-2-*p*-toluenesulfonylethyne (9).—**3k** (a mixture of both isomers, 3.64 g, 0.01 mol) and potassium carbonate (1.38 g, 0.01 mol) afforded 2.36 g (100%) of **9** (Table III).

1-Isopropyl-2-*p*-toluenesulfonylethyne (10).—**3i** (7.20 g, 0.02 mol) and potassium carbonate (2.76 g, 0.02 mol) afforded 2.70 g (61%) of **10** (Table III).

1-*n*-Butyl-2-ethanesulfonylethyne (11).—**5b** (4.53 g, 0.015 mol) and potassium carbonate (2.07 g, 0.015 mol) gave a pale yellow liquid which was subjected to vacuum distillation. There was obtained 0.81 g (31%) of **11** (Table III).

1-Phenyl-2-methanesulfonylethyne (12).—**4a** (30.81 g, 0.10 mol) and potassium carbonate (13.82 g, 0.10 mol) afforded 15.80 g (88%) of **12** (Table III).

1-Phenyl-2-ethanesulfonylethyne (13).—**5a** (29.00 g, 0.09 mol) and potassium carbonate (12.43 g, 0.09 mol) gave the product as a viscous yellow liquid. Drying under vacuum gave 19.09 g (theoretical yield was 17.39 g) of a product which was shown by nmr spectroscopy to be nearly pure acetylenic sulfone. Part of this oil was chromatographed on a silica gel column using a 1:3 mixture of chloroform–hexane as the eluent. Suitable fractions were collected and combined to give a sample for microanalysis.

1-Phenyl-2-isopropanesulfonylethyne (14).—**6** (6.72 g, 0.02 mol) and potassium carbonate (2.76 g, 0.02 mol) gave the product as a yellow oil. Chromatography on a silica gel column with hexane–chloroform (300 ml of a 4:1 mixture and then 300 ml of a 1:4 mixture) gave 2.16 g (52%) of **14** as a nearly colorless oil.

1-Phenyl-2-*tert*-butanesulfonylethyne (15).—**7** (3.40 g, 0.00971 mol) and potassium carbonate (1.34 g, 0.00971 mol) afforded 1.55 g (72%) of **15** (Table III).

***cis*-β-*p*-Toluenesulfonylstyrene.**—A solution of **3a** (19.21 g, 0.05 mol) and zinc (3.92 g, 0.06 g-atom) in acetic acid (4.80 g, 0.08 mol) and 5 ml of water was refluxed for 1.75 hr and allowed to cool. Water (500 ml) was added, and the resulting mixture was extracted with two 100-ml portions of chloroform. Evaporation of the solvent left a crude yellow oil, an nmr spectrum of which showed only the cis-substituted styrene to be present. This oil was dissolved in ethanol–water and, on cooling overnight, there was obtained 10.73 g (83%) of *cis*-β-*p*-toluenesulfonylstyrene, mp 75–76° (lit.[33] 76–77°).

***cis*-1-Cyclohexyl-2-*p*-toluenesulfonylethene.**—**3b** (7.81 g, 0.02 mol) and zinc (1.96 g, 0.03 g-atom) were combined in acetic acid (2.40 g, 0.04 mol) and 2 ml of water. After 1.5 hr of gentle reflux, the solution was treated as above. Again, nmr analysis of the crude oil showed only the reduced cis olefin. There was obtained 3.77 g (71%) of *cis*-1-cyclohexyl-2-*p*-toluenesulfonylethene, mp 50–51°.

Anal. Calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.63. Found: C, 68.39; H, 7.51.

***cis*-β-Methanesulfonylstyrene.**—When **4a** (3.08 g, 0.01 mol) and zinc (0.65 g, 0.01 g-atom) were combined as above with water (0.60 ml) and acetic acid (0.60 g, 0.01 mol), there was obtained 1.31 g of a clear, pale yellow oil. An nmr spectrum of this liquid was nearly identical with that of the known[34] *cis*-β-methanesulfonylstyrene. No trans product could be detected.

Pyrolysis of Acetylenic Sulfones.—The pyrolyses were carried out by two different methods. For compounds **12–14**, the sulfone was slowly dropped into a flask half filled with glass beads and immersed in an oil bath preheated to 250–270°. A vacuum distillation assembly was employed to distil the product as it was formed. For the pyrolysis of **15**, the acetylenic sulfone was gradually heated neat in a vacuum distillation apparatus.

1-Methyl-2-phenylethyne (16a).—**12** (10.81 g, 0.06 mol) gave 2.76 g (40%) of **16a**, bp 79–81° (15 mm) [lit.[35] bp 74–75° (14 mm)].

1-Ethyl-2-phenylethyne (16b).—**13** (11.66 g, 0.06 mol) afforded 5.28 g (68%) of **16b**, bp 96–100° (45 mm) [lit.[30] bp 87–90° (18 mm)].

1-Isopropyl-2-phenylethyne (16c).—**14** (10.35 g, 0.0502 mol), on pyrolyzing at 270°, gave 6.48 g of distillate which proved to be a mixture of starting material and product. Redistillation afforded 4.76 g (66%) of pure **16c**, bp 99–101° (20 mm) [lit.[36] bp 88–89° (10 mm)].

1-*tert*-Butyl-2-phenylethyne (16d).—**15** (0.90 g, 0.00405 mol), when heated with several glass beads, began to decompose at a bath temperature of *ca.* 150° (the product began to distil), and, by the time a temperature of 200° was reached, the extrusion was complete. There was collected 0.64 g (73%) of **16d**, bp 93–96° (20 mm) [lit.[36] bp 84° (10 mm)].

General Procedure for Coupling of Cuprous Phenylacetylide with Iodovinyl Sulfones.—The sulfone and acetylide[22] were combined in 100 ml of dry pyridine and the solution was refluxed 15 hr. The cooled mixture was poured into 300 ml of water and extracted three times with 150-ml portions of ether. The combined ether extracts were then washed twice each with water, dilute hydrochloric acid, water, dilute sodium bicarbonate solution, and finally water again. The organic layer was dried

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over magnesium sulfate and decolorized with activated charcoal. Solvent removal gave the crude product.

2,4-Diphenyl-1-*p*-toluenesulfonylbut-1-en-3-yne (17c).—From **3a** (7.68 g, 0.02 mol) and cuprous phenylacetylide (3.29 g, 0.02 mol) there was obtained 1.05 g (15%) of **17c**, mp 117–118°.

Anal. Calcd for $C_{23}H_{18}O_2S$: C, 77.07; H, 5.06; S, 8.94. Found: C, 77.33; H, 5.00; S, 8.96.

2,4-Diphenyl-1-ethanesulfonylbut-1-en-3-yne (17b).—**5a** (6.44 g, 0.02 mol) and the acetylide (3.29 g, 0.02 mol) afforded 3.47 g (59%) of **17b**, mp 76–77°.

Anal. Calcd for $C_{18}H_{16}O_2S$: C, 72.99; H, 5.44; S, 10.82. Found: C, 73.08; H, 5.60; S, 10.58.

4-Phenyl-2-cyclohexyl-1-*p*-toluenesulfonylbut-1-en-3-yne (17a).—When **3c** (7.81 g, 0.02 mol) and the acetylide (3.29 g, 0.02 mol) were combined as before, a viscous yellow oil was obtained (5.84 g, 80%) which could not be induced to solidify. The ir and nmr spectra of this oil were identical with those obtained on the pure product (see the following). A portion of this oil was then chromatographed on a silica gel column using chloroform–hexane (1:1) as the eluent. Again, the same viscous, yellow oil was encountered and, after vacuum drying, it was analyzed as such.

Anal. Calcd for $C_{23}H_{24}O_2S$: C, 75.78; H, 6.64; S, 8.80. Found: C, 75.79; H, 6.83; S, 8.92.

Registry No.—**3a**, 22183-12-6; **3b**, 22214-91-1; **3c**, 22297-38-7; **3d**, 29038-88-8; **3e**, 28995-73-5; **3f**, 28995-74-6; **3g**, 28995-75-7; **3h**, 28995-76-8; **3i**, 28995-77-9; **3j**, 28995-78-0; *trans*-**3k**, 28995-79-1; *cis*-**3k**, 22214-90-0; **3l**, 22214-94-4; **3m**, 22214-93-3; **3n**, 22214-92-2; **4a**, 28995-82-6; **4b**, 28995-83-7; **5a**, 28995-84-8; **5b**, 28995-85-9; **6**, 28995-86-0; **7**, 28995-87-1; **8**, 28995-88-2; **9**, 28995-90-6; **10**, 28995-91-7; **11**, 28995-92-8; **12**, 24378-05-0; **15**, 28995-94-0; **17b**, 28995-95-1; **17c**, 28995-96-2; *cis*-1-cyclohexyl-2-*p*-toluenesulfonylethene, 28995-97-3.

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Reaction of Carbethoxycarbene with Aliphatic Sulfides and Allyl Compounds

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Reactions of carbethoxycarbene produced by photolysis of ethyl diazoacetate with dialkyl and alkyl allyl sulfides were investigated. Reactions in dialkyl sulfides bearing β-hydrogen atoms resulted in the formation of ethyl alkylmercaptoacetates. On the other hand, the reactions in alkyl allyl sulfides gave mixtures of 1-alkyl 1-alkylmercaptoacetates (C—S insertion) and cyclopropane derivatives (C=C addition). These product formations are explained by the mechanism involving ylide formation from the carbene and sulfides. Copper-catalyzed thermal decomposition of ethyl diazoacetate in these sulfides resulted in more selective reactions and gave high yields of the acetates, the formation of cyclopropane derivatives being drastically reduced. Allyl ethers and chlorides react less selectively with carbethoxycarbene to produce mixtures of insertion and addition products.

Although the reactions of carbenes with molecules containing heteroatoms have been extensively studied, little has been recorded of the photochemical and thermal reactions with aliphatic sulfides and allyl compounds containing sulfur, oxygen, and halides.[1] Some of the reactions of the allyl compounds have been reported with dichlorocarbene derived from the acid–base-catalyzed reaction of the halo ester[2] and with methylene produced by the decomposition of diazomethane with metal salts.[3] Kirmse has reported that the copper salt catalyzed thermal decomposition of diazomethane in allyl sulfides yields methylene insertion products into the carbon–sulfur bond as major products, together with some cyclopropane derivatives. In the allyl ethers and amines, however, the cyclopropane derivatives have been obtained as the major products. Furthermore, the addition products have been formed from allyl chlorides without substantial formation of insertion products. This is contrasted with the reaction in allyl bromide in which the insertion product has been obtained in about 80% yield. The formation of insertion products may be ascribed to ylide formation by the attack of the carbene on the lone-pair electrons of a heteroatom, followed by allylic rearrangement which is a thermally symmetry-allowed process. Similar results in the copper-catalyzed thermal decomposition of ethyl diazoacetate in allyl halides have been obtained. Thus, the addition of the carbene to the double bond in allyl chlorides competes effectively with insertion into the carbon–chlorine bond, whereas no cyclopropanes have been obtained from allyl bromides and iodides.[4,5] However, these reaction species have been known as carbenoids and should be significantly different in nature from the free carbenes formed by photolysis of the diazo compounds.[6–8]

Recently we reported that the photochemical reaction of dimethyl diazomalonate in aliphatic sulfides forms stable sulfonium ylides[9] and in allyl compounds forms the carbene insertion products into the carbon–sulfur, oxygen, and halogen bond.[10,11] We have sug-

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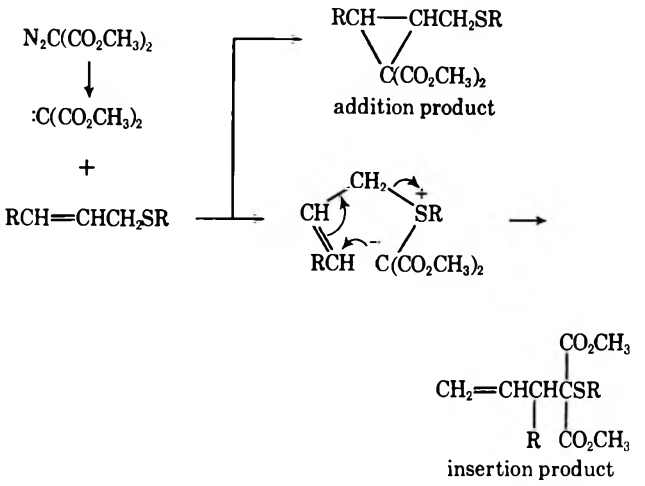
gested that the insertion products were formed as proceeding *via* [1,5] sigmatropic allylic rearrangement of intermediate ylides.



The study was extended to the photochemical reaction of diazoacetate, where the carbene formed by the photolysis is considered to be less electrophilic, and ylides formed by the reaction of the carbene with heteroatom-containing molecules are expected to be less resonance stabilized compared with the case of the reaction of diazomalonate.

Results

Irradiation of a solution of ethyl diazoacetate in a relevant substrate was carried out in a Pyrex tube with a high-pressure mercury lamp. The reaction mixture was analyzed by vpc, and the structures of the isolated products were determined on the basis of nmr and ir spectra and elemental analysis.

Reactions with Aliphatic Sulfides.—Photochemical decomposition of ethyl diazoacetate in di-*tert*-butyl sulfide produced 23% ethyl *tert*-butylmercaptoacetate. Similarly, the reaction in diethyl sulfide gave ethyl ethylmercaptoacetate, although the yield was reduced. Each product was identified by comparison of its spectra with that of the authentic sample. On the other hand,

$$N_2CHCO_2C_2H_5 + \textit{tert}\text{-BuS-}\textit{tert}\text{-Bu} \longrightarrow \underset{23\%}{\textit{tert}\text{-BuSCH}_2CO_2C_2H_5}$$

$$N_2CHCO_2B_2H_5 + EtSEt \longrightarrow \underset{7\%}{EtSCH_2CO_2C_2H_5}$$

the reaction in dimethyl sulfide gave only tarry materials and no product detectable by gas chromatographic analysis.

$$N_2CHCO_2C_2H_5 + CH_3SCH_3 \longrightarrow \text{tarry materials}$$

Reactions with Allyl Sulfides.—Thermal and photochemical decomposition of ethyl diazoacetate in allyl sulfides produced insertion and addition products. The dependence of the yield on the reaction variables is summarized in Table I. The starting allyl sulfides and the products were stable under the conditions employed in the reactions and the analytical procedures.

In the reaction of I with carbethoxycarbene, no significant difference in the product distribution was observed between the thermal and photochemical decomposition, although thermolysis gave only 30% decomposition of ethyl diazoacetate under the conditions.

TABLE I

DEPENDENCE OF PRODUCT DISTRIBUTION ON REACTION VARIABLES

Sulfide	Diazoacetate, mmol	Mode of decompn	A (addition) (cis + trans), %	B (insertion), %
I	1.8	$h\nu$	6	23
I	1.9	$h\nu$	7	19
I	1.8	CuCl, 90° (2 min)		95
I	1.8	Cu, 90° (2 hr)		85
I	2.0	80°, 24 hr[a]	5	25
II	4.4	$h\nu$	10	15
III	4.4	$h\nu$	13	16
IV	4.4	$h\nu$	15	23

[a] 30% of diazoacetate was decomposed under these conditions.

On the other hand, the copper-catalyzed thermal decomposition was remarkable both in high reaction rate and in increased yields of insertion products. The

$$:CHCO_2C_2H_5 + R^1CH{=}CR^2CH_2SR^3 \longrightarrow$$

$$\underset{\text{A (addition)}}{R^1CH(CHCO_2C_2H_5)CR^2CH_2SR^3} + \underset{\text{B (insertion)}}{CH_2{=}CR^2CH(CO_2C_2H_5)CHSR^3(R^1)}$$

I, $R^1 = CH_3$; $R^2 = H$; $R^3 = C_2H_5$
II, $R^1 = R^2 = H$; $R^3 = n$-Bu
III, $R^1 = R^2 = H$; $R^3 = tert$-Bu
IV, $R^1 = H$; $R^2 = CH_3$; $R^3 = n$-Bu

structure of the insertion product obtained from I was established to be IB by the analysis of nmr and ir spectra. Absence of the nonrearranged insertion product in the reaction mixture was proved by gas chromatography. The elimination product, ethyl γ-methylallylmercaptoacetate, was also found not to be produced.

Reactions with Allyl Ethers.—Reaction products of carbethoxycarbene with allyl methyl ethers are tabulated in Table II. Analogous to the reactions with

TABLE II

REACTIONS OF CARBETHOXYCARBENE WITH ALLYL METHYL ETHERS

Ether	Diazoacetate, mmol	Mode of decompn	A[a] (addition), %	B (insertion), %	C (insertion), %
V	1.5	$h\nu$	19.5	19.5	
V	1.5	$CuSO_4$[b]	25.0	45.8	
VI	0.95	$h\nu$	15.2	4.5	21.8
VI	0.95	$CuSO_4$	10.4	2.7	32.0

[a] The mixture of cis and trans cyclopropanes. [b] Copper sulfate catalyzed thermal reaction was carried out at 105° for 5.5 hr.

allyl sulfides, the insertion and addition products were mainly produced. However, the product distribution shows that the carbene attacked less favorably on oxygen atoms, compared with the reaction with allyl sulfides. It is noteworthy that, even in the copper salt catalyzed reaction, considerable amounts of addition products were formed.

Furthermore, a small percentage of the direct insertion product, namely VIB, was detected in the reaction mixture of VI. Although the possibility that this

direct insertion product originates from α-methylallyl methyl ether, which exists in a small amount in the starting ether, might not be eliminated, at least a part of VIB should be considered to form from VI, since the yield of this acetate was much more than that expected from α-methylallyl methyl ether contaminating the starting material (less than 0.5%).

$$:CHCO_2C_2H_5 + RCH{=}CHCH_2OCH_3 \longrightarrow$$

$$RCH(CHCO_2C_2H_5)CH_2OCH_3 \ (A) + RCH{=}CHCH(CO_2C_2H_5)CHOCH_3 \ (B) +$$

$$CH_2{=}C(R)CHCHCHOCH_3 \ (C), \quad CO_2C_2H_5$$

V, R = H; VI, R = CH_3

Reactions with Allyl Chlorides.—Carbethoxycarbene produced by photolysis of ethyl diazoacetate reacted with allyl chloride to give 21% allyl chloroacetate and 18% cyclopropane derivatives. With IX, the formation of ethyl γ-methylallylchloroacetate (IXB), besides cyclopropane derivatives IXA and ethyl α-methylallylchloroacetate IXC, was observed contrasting to bis(carbomethoxy)carbene which did not give methyl α-methylallylchloromalonate. Since the starting IX, which contains less than 0.5% α-methyl allyl chloride, and the products were stable to the reaction conditions and to the analytical procedures, the direct insertion product (A) should be considered to actually form through the reaction of carbethoxycarbene with IX (Table III).

$$:CHCO_2C_2H_5 + R^1CH{=}CR^2CH_2Cl \longrightarrow$$

$$R^1CH(CHCO_2C_2H_5)CR^2CH_2Cl \ (A) + R^1CH{=}CR^2CH_2CHCl(CO_2C_2H_5) \ (B) +$$

$$CH_2{=}C(R^1)CHCHCl(CO_2C_2H_5) \ (C) + CHClCO_2C_2H_5 \ (D) + (CHCO_2C_2H_5)_2 \ (E + F)$$

VII, $R^1 = R^2 = H$; VIII, $R^1 = H$, $R^2 = CH_3$; IX, $R^1 = CH_3$, $R^2 = H$

Discussion

In contrast to bis(carbomethoxy)carbene which reacts with a number of alkyl sulfides to give stable ylides,[9] carbethoxycarbene did not, but afforded the products which are considered to be produced by further reaction of the corresponding ylides. This may be partly due to less thermal stabilities of ylides formed by the reaction of carbethoxycarbene with sulfides, compared with those derived from bis(carbomethoxy)carbene.

Dimethylsulfonium carbethoxymethylide has been known as an isolable compound at low temperature.[12] Nevertheless, the isolation of the ylide was unsuccessful even when photochemical reaction of ethyl diazoacetate in dimethyl sulfide was carried out at low temperature. Perhaps a nascent ylide molecule, derived from sulfide and the carbene produced photochemically, has enough excess energy to allow a less stable ylide molecule to react.

TABLE III

REACTION OF ETHYL DIAZOACETATE WITH ALLYL CHLORIDES

Chloride	Diazoacetate, mmol	Mode of decompn	Products, % A[a]	B	C	D	E[b]	F[c]
VII	1.8	hν	18	21		t[d]	t	t
VIII	1.8	hν	57	30		t	t	t
IX	1.8	hν	8	9	7	2	t	t
IX	1.9	CuCl, 80° (60 min)	2	1	8	4	40	22
IX	1.8	CuCl, 80° (9 min)	3	1	11	5	37	22
IX	1.9	Cu, 80° (60 min)	3	2	4	3	37	22

[a] The mixture of cis and trans cyclopropanes. [b] Ethyl fumarate. [c] Ethyl maleate. [d] t = trace amount.

The reactions with alkyl sulfides bearing β-hydrogen atoms gave β-elimination products (alkyl mercaptoacetate). These are considered to form by thermally induced intramolecular elimination. Although olefins were not detected, their formations may be almost certain, since similar eliminations involving cleavage of C–O or C–N bonds have been well known in the reactions of carbenes with ethyl ether, *n*-butyl ether, and trimethylamine.[1]

Furthermore, the intermediary formation of an ylide is supported by the fact that similar elimination actually occurs on the thermolysis of alkylsulfonium bis(carbomethoxy)methylide.[13]

$$:CHCO_2C_2H_5 + EtSEt \longrightarrow$$

$$EtS^+(CH_2)CH(CO_2C_2H_5)CH_2 \longrightarrow EtSCH_2CO_2C_2H_5$$

The formation of rearranged insertion products in the reactions of the carbene with allylic compounds is also explained in terms of the ylide mechanism, as has been suggested for the similar reactions of dimethyl diazomalonate. The relative rate of insertion to addition can be seen to depend on nucleophilic characters of heteroatoms (S > O > Cl) of allylic compounds. This trend may be consistent with the idea that ylides are produced by electrophilic attack of the carbene on heteroatoms in the substrates. Copper-catalyzed reactions favored more selectively the insertion compared with photochemical reactions. This may be due to the fact that the attacking species in copper-catalyzed reactions are Cu-complexed carbenoid which are more selective and electrophilic than the free carbenes.

This insertion accompanying allylic rearrangement may be essentially a [1,5] sigmatropic rearrangement of an ylide which is expected to occur quite smoothly, since the process is orbital symmetry allowed in thermal reaction. Indeed, a number of examples of such rearrangements of unstable ylides have been reported.[14,15]

(12) A. J. Speziale, C. C. Tung, K. W. Ratts, and A. Yao, *J. Amer. Chem. Soc.*, **87**, 3460 (1965).

(13) W. Ando, T. Yagihara, and T. Migita, *Tetrahedron Lett.*, 1975 (1969).

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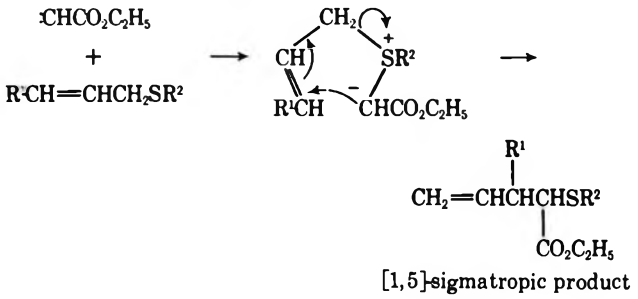
(15) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 2511 (1965), and references cited therein.

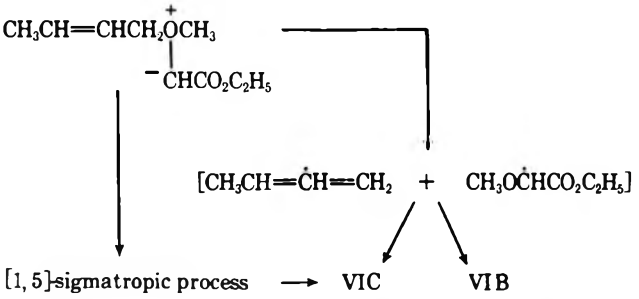
The reaction of carbethoxycarbene with I gave this [1,5] sigmatropic product but not the β-elimination product. This is in accord with the fact that bis(carbomethoxy)carbene did not give any isolable ylides in the reaction with allylic sulfides,[10] contrasting with the reaction with saturated aliphatic sulfides, and indicates that [1,5] sigmatropic rearrangement of the ylide occurs much more smoothly than intramolecular elimination.



[1,5]-sigmatropic product

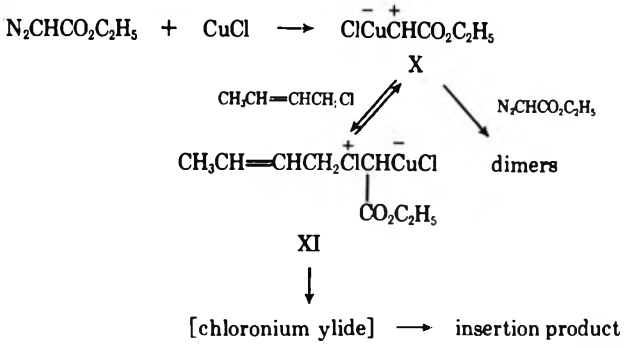
A notable feature of the reactions of carbethoxycarbene with allylic ether or chloride is the formation of nonrearranged insertion products, which were observed neither in the reactions with allylic sulfides nor in the reactions of bis(carbomethoxy)carbene with allylic sulfides and ethers.

One of the tentative mechanisms for the formation of these nonrearranged products seems to be a dissociation–recombination process, since the concerted mechanism of such a [1,3] sigmatropic rearrangement of ylide is orbital symmetry forbidden in thermal reactions. Although we have no experimental evidence which is useful in distinguishing whether the dissociation is heterolytic or homolytic, the homolytic process seems to be more likely, since several chemically induced dynamic nuclear polarization (CIDNP) observations have been reported on the formation of [1,3] sigmatropic products in the thermal rearrangement of a sulfonium ylide formed from a sulfonium salt and base.[16] As



mentioned above, an ylide molecule is considered to have excess energy at a moment of the formation from a carbene and heteroatomic molecule. If this excess energy is enough for the dissociation of ylide, and if the dissociation is fast enough to compete with collisional deactivation of the ylide molecule, the [1,3] sigmatropic rearrangement will become a possible pathway involving a radical-pair intermediate. On the other hand, if the activation energy of the dissociation exceeds the excess energy, the [1,3] sigmatropic process would not occur. Sulfonium ylides are resonance stabilized by pπ–dπ conjugation, and the negative charge of bis(carbomethoxy)methylide is stabilized by the resonance effect of two carbomethoxy groups. Dissociation of these relatively highly stabilized ylides will require high activation energy. On the other hand, the relatively unstable oxonium and chloronium carbethoxymethylides will dissociate with less activation energy, converting to [1,3] sigmatropic products by recombination of a radical pair.

The copper-catalyzed thermal reaction of ethyl diazoacetate with allyl chloride gave the carbene dimers as major products in contrast to no formation of carbene dimers in the reaction with allyl sulfides and ethers. A possible pathway is proposed involving the decomposition of the Cu-complexed chloronium compound XI to the carbenoid X rather than the formation of the chloronium ylide, followed by the reaction of X with ethyl diazoacetate leading to the dimers.



Experimental Section

General.—Infrared spectra were determined on a Japan spectroscopic Co., Ltd., DS-21 instrument in carbon tetrachloride solution or neat. The nmr spectra were recorded on Varian A-60D spectrometer using carbon tetrachloride solutions containing tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (ppm) downfield from TMS, designating the multiplicity of the signals: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Samples of ethyl diazoacetate were added to clean 10 × 100 mm Pyrex tubes. The tubes were then corked (nondegassed) and placed in a water-cooled bath for irradiation. The light source was a 400-W Rikosha high-pressure mercury lamp having the maximum output at 3650–3660 Å with the minor output at 3125 Å. Photolyses were carried out until the disappearance of diazo band in the infrared spectra. The solutions were analyzed on an Ohkura gas–liquid partition chromatograph with a calibrated 5 ft × 0.25 in. stainless steel column of 10% DC-710 or Carbowax 20M on C-22 firebrick. Hydrogen was used as a carrier gas. Absolute yields were estimated from the relative area of peaks of products to known amounts of appropriate internal standards.

Materials.—Research grade reagents of dimethyl sulfide and di-*tert*-butyl sulfide (Tokyo Kasei), allyl chloride, β-methylallyl chloride, and γ-methylallyl chloride (Wako Fine Chemicals) were used without further purification. Diethyl sulfide was prepared by the addition of ethyl bromide to an ethyl alcohol solution of sodium metal and ethyl mercaptan. The fraction boiling at 92–93° was collected for use. All of the allyl sulfides and ethers were prepared by standard procedures.[17,18] Ethyl diazoacetate[19] was prepared by treating ethyl glycinate hydrochloride with sodium nitrile, bp 36–36.5° (9 mm).

General Procedure of Photochemical Reactions of Ethyl Diazoacetate.—Photolysis of 0.32 g (2.8 mmol) of ethyl diazo-

(16) (a) U. Schöllkopf, G. Ostermann, and J. Schossing, *Tetrahedron Lett.*, 2619 (1969); (b) A. R. Lepley, *J. Amer. Chem. Soc.*, **91**, 1237 (1969); **91**, 1237 (1969); (c) R. W. Jemison and D. G. Morris, *Chem. Commun.*, 1226 (1969); (d) D. G. Morris, *ibid.*, 1345 (1969).

(17) A. A. Oswald, K. Griesbaum, W. A. Thaler, and B. E. Hudson, Jr., *J. Amer. Chem. Soc.*, **84**, 3897 (1962).

(18) W. H. Watanabe, L. E. Conlon, and J. C. H. Hwa, *J. Org. Chem.*, **23**, 1666 (1958).

(19) N. E. Searle "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 424.

acetate in 3 ml of a substrate was carried out with a high-pressure mercury lamp. After the diazo band disappeared from the reaction mixture, a known amount of an internal standard (phenyltriethylsilane) was added to the reaction mixture, which was then analyzed by gas chromatography. The structure of the isolated product was determined on the basis of nmr and ir spectra data and elemental analysis. The cyclopropane derivatives obtained from the reaction with the allyl system consist of two geometrical isomers. Their configurations were not assigned. Analytical data are summarized (A-1 and A-2 are stereoisomers of cyclopropane products).

IA-1: nmr 1.25 (m, 12 H), 2.48 (m, 4 H), 4.10 (q, 2 H); ir 1725 cm^{-1}. *Anal.* Calcd for $C_{10}H_{18}O_2S$: C, 59.38; H, 8.97. Found: C, 58.67; H, 8.81.

IA-2: nmr 1.25 (m, 11 H), 1.68 (m, 1 H), 2.50 (q, 2 H), 2.70 (m, 2 H), 4.10 (q, 2 H); ir 1725 cm^{-1}. *Anal.* Calcd for $C_{10}H_{18}O_2S$: C, 59.38; H, 8.97. Found: C, 59.91, H, 8.92.

IB: nmr 1.18 (m, 9 H), 2.55 (q, 2 H), 2.66 (m, 1 H), 2.96 (d, 1 H), 4.13 (q, 2 H), 5.01 (broad m, 2 H), 5.66 (m, 1 H); ir 930, 980, 1635, 1750 cm^{-1}. *Anal.* Calcd for $C_{10}H_{18}O_2S$: C, 59.38; H, 8.97. Found: C, 59.55; H, 9.17.

IIA: nmr 1.25 (m, 14 H), 2.42 (m, 2 H), 4.03 (q, 2 H); ir 1725, 1746 cm^{-1}. *Anal.* Calcd for $C_{22}H_{20}O_2S$: C, 61.09; H, 9.32. Found: C, 61.55; H, 9.35.

IIB: nmr 0.92 (t, 3 H), 1.26 (t, 3 H), 1.44 (m, 4 H), 2.51 (t, 2 H), 3.10 (m, 3 H), 4.13 (q, 2 H), 5.03 (broad d, 2 H), 5.80 (m, 1 H); ir 920, 1645, 1735 cm^{-1}. *Anal.* Calcd for $C_{11}H_{20}O_2S$: C, 61.09; H, 9.32. Found: C, 61.39; H, 9.56.

IIIA-1: nmr 1.25 (m, 7 H), 1.29 (s, 9 H), 2.50 (center of two d, 2 H), 4.05 (q, 2 H); ir 1725 cm^{-1}. *Anal.* Calcd for $C_{11}H_{20}O_2S$: C, 61.09; H, 9.32. Found: C, 60.86; H, 8.95.

IIIA-2: nmr 1.28 (m, 7 H), 1.29 (s, 9 H), 2.70 (center of two d, 2 H), 4.10 (q, 2 H); ir 1725 cm^{-1}. *Anal.* Calcd for $C_{11}H_{20}O_2S$: C, 61.09; H, 9.32. Found: C, 60.96; H, 8.95.

IIIB: nmr 1.25 (t, 3 H), 1.34 (s, 9 H), 2.40 (m, 2 H), 3.18 (center of two d, 1 H), 4.12 (q, 2 H), 5.02 (broad d, 2 H), 5.72 (m, 1 H); ir 925, 1645, 1730 cm^{-1}. *Anal.* Calcd for $C_{11}H_{20}O_2S$: C, 61.09; H, 9.32. Found: C, 61.07; H, 9.14.

IVA: nmr 0.97 (m, 3 H), 1.23 (s, 3 H), 1.26 (t, 3 H), 1.58 (m, 7 H), 2.45 (m, 2 H), 2.70 (s, 2 H), 4.10 (q, 2 H); ir, 1716 cm^{-1}. *Anal.* Calcd for $C_{12}H_{22}O_2S$: C, 62.58; H, 9.63. Found: C, 62.63; H, 9.51.

IVB: nmr 0.95 (t, 3 H), 1.25 (t, 3 H), 1.50 (m, 4 H), 1.73 (s, 3 H), 2.50 (m, 4 H), 3.28 (center of two d, 1 H), 4.11 (q, 2 H), 4.72 (m, 2 H); ir 895, 1655, 1725, 1745 cm^{-1}. *Anal.* Calcd for $C_{12}H_{22}O_2S$: C, 62.58; H, 9.63. Found: C, 62.84; H, 9.61.

VA: nmr 1.25 (t, 3 H), 1.53 (m, 4 H), 3.26 (s, 3 H), 3.28 (m, 2 H), 4.08 (q, 2 H); ir 1730 cm^{-1}. *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.77; H, 9.06.

VB: nmr 1.30 (t, 3 H), 2.41 (m, 2 H), 3.33 (s, 3 H), 3.66 (t, 1 H), 4.15 (q, 2 H), 4.98 (broad d, 2 H), 5.55 (m, 1 H); ir 916, 1643, 1740, 1755 cm^{-1}. *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.98; H, 8.86.

VIA-1: nmr 1.27 (m + t, 9 H), 3.20 (s, 3 H), 3.45 (m, 2 H), 4.06 (q, 2 H); ir 1725 cm^{-1}. *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 63.09; H, 9.42.

VIA-2: nmr 1.27 (m + t, 9 H), 3.25 (m + s, 5 H), 4.08 (q, 2 H); ir 1725 cm^{-1}. *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.33; H, 9.09.

VIB: nmr 1.27 (t, 3 H), 1.73 (d, 3 H), 2.33 (center of two d, 2 H), 3.24 (d, 3 H), 3.53 (m, 1 H), 4.08 (q, 2 H), 5.45 (m, 2 H); ir 966, 1675, 1742 cm^{-1}. *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.89; H, 9.55.

VIC: nmr 1.03 (d, 3 H), 1.28 (t, 3 H), 2.50 (m, 1 H), 3.30 (s, 3 H), 3.48 (d, 1 H), 4.15 (q, 2 H), 4.91 (broad d, 2 H), 5.65 (m, 1 H); ir 915, 1640, 1735, 1754 cm^{-1}. *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 63.08; H, 9.52.

VIIA-1: nmr 1.13 (m, 2 H), 1.28 (t, 3 H), 1.80 (m, 2 H), 3.72 (center of two d, 2 H), 4.12 (q, 2 H). *Anal.* Calcd for $C_7H_{11}ClO_2$: C, 51.69; H, 6.76. Found: C, 51.37; H, 6.72.

VIIA-2: nmr 1.26 (t + m, 5 H), 1.58 (m, 2 H), 3.45 (s, 2 H), 4.10 (q, 2 H). *Anal.* Calcd for $C_7H_{11}ClO_2$: C, 51.69; H, 6.76. Found: C, 51.56; H, 6.98.

VIIB,C: nmr 1.30 (t, 3 H), 2.67 (m, 2 H), 4.21 (q + t, 3 H), 5.12 (broad d, 2 H), 5.68 (m, 1 H). *Anal.* Calcd for $C_7H_{11}ClO_2$: C, 51.69; H, 6.76. Found: C, 51.75; H, 7.12.

IXA-1: nmr 1.26 (t + d + m, 9 H), 3.72 (center of two d, 2 H), 4.10 (q, 2 H); ir 1730 cm^{-1}. *Anal.* Calcd for $C_8H_{13}ClO_2$: C, 54.36; H, 7.36. Found: C, 54.90; H, 7.40.

IXA-2: nmr 1.26 (t + d, 6 H), 1.54 (m, 3 H), 3.45 (d, 2 H), 4.10 (q, 2 H); ir 1730 cm^{-1}. *Anal.* Calcd for $C_8H_{13}ClO_2$: C, 54.36; H, 7.36. Found: C, 54.09; H, 7.55.

IXB: nmr 1.30 (t, 3 H), 1.68 (d, 3 H), 2.60 (m, 2 H), 4.10 (t, 1 H), 4.18 (q, 2 H), 5.54 (m, 2 H); ir 965, 1745 cm^{-1}. *Anal.* Calcd for $C_8H_{13}ClO_2$: C, 54.36; H, 7.36. Found: C, 53.78; H, 7.23.

IXC: nmr 1.18 (t, 3 H), 1.28 (t, 3 H), 2.75 (m, 1 H), 3.96 (d, 1 H), 4.16 (q, 2 H), 5.09 (broad d, 2 H), 5.70 (m, 1 H); ir 940, 975, 1745 cm^{-1}. *Anal.* Calcd for $C_8H_{13}ClO_2$: C, 54.36; H, 7.36. Found: C, 54.77; H, 7.76.

General Procedure of Copper Salt Catalyzed Thermal Reactions.—Thermal reactions were carried out for 0.17 g (1.5 mmol) of ethyl diazoacetate in 2 ml of a substrate in the presence of 20 mg of copper salt. Samples were sealed in Pyrex tubes under vacuum and heated at 100° for the appropriate time.

Registry No.—IA, 29123-96-4; IB, 29123-97-5; IIA, 29123-98-6; IIB, 29123-99-7; IIIA-1, 29119-66-2; IIIA-2, 29199-37-9; IIIB, 29124-00-3; IVA, 29124-01-4; IVB, 29124-02-5; VA, 29124-03-6; VB, 29124-04-7; VIA, 29124-05-8; VIB, 29119-67-3; VIC, 29119-68-4; VIIA, 29119-69-5; VIIB, 29119-70-8; IXA, 29119-71-9; IXB, 29119-72-0; IXC, 29119-38-0; carbethoxycarbene, 3315-61-5.

Conformations of Certain Acyclic Sulfoxide Alcohols

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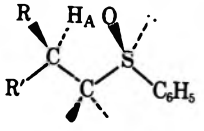
Received August 14, 1970

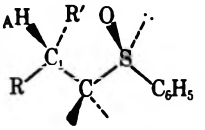
The nmr parameters of the four isomeric 1,2-diphenyl-2-phenylsulfinyl-1-ethanols are compared to the respective sulfides and sulfones. The greatest steric change occurs in going to the sulfoxide indicating that the sulfur oxygen is relatively more space demanding than the nonbonded pair. Hydroxyl splittings due to internal hydrogen bonding are discussed, and it is shown that the intramolecular hydrogen bond to the sulfoxide is less stable than the intermolecular hydrogen bond to DMSO. An instance of large long-range coupling to hydroxyl is given.

In several six-membered rings containing the sulfoxide group, the oxygen function has been shown to preferentially occupy the axial orientation.[1-6] However, the possibility that oxygen is less space demanding than the nonbonded pair at sulfur does not seem reasonable. The opinion has been expressed that an attractive interaction exists between the axial oxygen and the axial hydrogens at C-3 and C-5.[2] This viewpoint has been supported by calculations of conformer energies by the Westheimer method.[7] Recently, however, Johnson and Siegl reported a preference by sulfinyl oxygen for the pseudoequatorial position in a four-ring sulfoxide.[8]

In acyclic sulfoxides, such as **1**, molecular models suggest a preference by the *S*-phenyl group for the position shown, because of the acute C–S–phenyl bond angle (*ca.* 96°).[9] In studies of acyclic molecules, 1,3 interactions, similar to 1,3-diaxial interactions in a cyclohexane system, are usually very unfavorable.[10,11] Thus, an attractive interaction between oxygen and the C-1 hydrogen in conformer **1′** and/or a repulsive interaction between oxygen and R in conformer **1**, should stabilize **1′** compared to **1**.



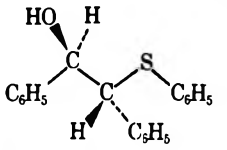
1



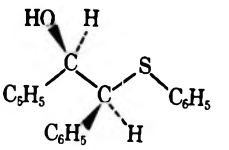
1′

The purpose of the present work is to study the conformational preferences of a series of sulfur-containing alcohols, with consideration given to the preferred orientation of major groups at sulfur. The compounds of interest (Chart I) include the isomeric sulfides **2** and **3**, which have only nonbonded electrons at sulfur, the four isomeric sulfoxides **4**–**7**, and the sulfones **8** and **9** which have two oxygens at sulfur. The structures shown (Chart I) imply predominant conformation as well as configuration at carbon. Configuration (not conformation) is implied for **5**–**7** at sulfur. In addition, the simpler alcohols **10** and **11** as well as **12** will be concidered briefly. The synthesis of compounds **2**–**9** will be covered in a later paper.

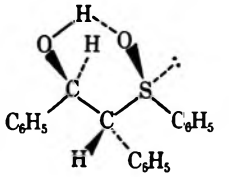
CHART I



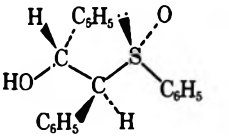
2 (threo)



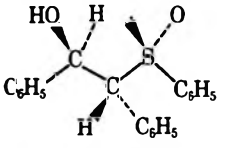
3 (erythro)



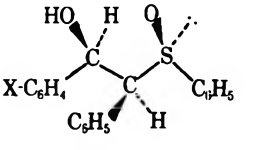
4 (threo)



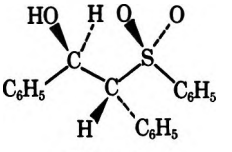
6 (erythro)



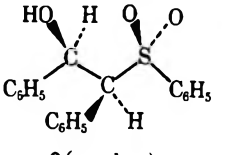
5 (threo)



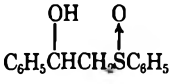
7 (erythro) **a**, X = H; **b**, X = Cl



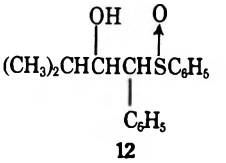
8 (threo)



9 (erythro)



10, **11**



12

As Chapman and King[12] have shown, exchange of the hydroxyl proton is slowed in dimethyl sulfoxide (DMSO) solution due to strong hydrogen bonding. The slow exchange permits observation of couplings to the hydroxyl proton. Thus, in **1**, if R is hydroxyl, hydrogen bonded to the sulfinyl oxygen, a doublet hydroxyl resonance should be observed in chloroform. In any other conformation at sulfur, such coupling would be much less probable. Admittedly the possibility of a strong intramolecular hydrogen bond would

(1) J. C. Martin and J. Uebel, *J. Amer. Chem. Soc.*, **86**, 2936 (1964).
(2) C. R. Johnson and D. McCants, Jr., *ibid.*, **86**, 2935 (1964); **87**, 110 (1965).
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(4) P. B. D. de la Mare, D. J. Millen, J. G. Tillett, and D. Watson, *ibid.*, 1619 (1963).
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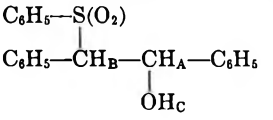
(6) D. G. Hellier, J. G. Tillett, H. F. Van Woerden, and R. F. M. White, *Chem. Ind. (London)*, 1958 (1963).
(7) N. L. Allinger, J. A. Hirsch, and M. A. Miller, and I. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).
(8) C. R. Johnson and W. O. Siegl, *ibid.*, **91**, 2796 (1969).
(9) D. Martin, A. Weise, and H. J. Niclas, *Angew. Chem., Int. Ed. Engl.* **6**, 318 (1967).
(10) A. Dempster, K. Price, and N. Sheppard, *Chem. Commun.*, 1457 (1968).
(11) C. A. Kingsbury and D. C. Best, *J. Org. Chem.*, **33**, 3252 (1968).
(12) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

TABLE I
NMR CHEMICAL SHIFTS AND COUPLING CONSTANTS



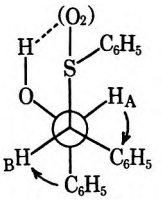
Compd	Mp, °C	Chemical shifts, ppm: H_A ($CDCl_3$)	H_B ($CDCl_3$)	H_A (TFA)	H_B (TFA)	J_{AB} (J_{AC}) in Hz, $CDCl_3$: 10%	5%	2.5%	1.3%	J_{AB} (J_{AC}) in Hz, DMSO
Sulfide										
2, threo[b]	76	4.94	4.35			8.6	8.6 (*ca.* 2.0)	8.6 (*ca.* 2.0)	8.7 (*ca.* 2.0)	6.0
3, erythro[b]	92	5.04	4.44				6.1 (3.8)	6.2 (3.6)	5.8 (*ca.* 3.0)	6.3 (4.8)
Sulfoxide										
4, threo	129	5.64	3.94	5.97	4.68	9.5	9.5 (1.8)	9.6 (1.8)	9.7	9.2 (4.2)
5, threo	196	5.62	3.95	5.91	4.61	*a*	*a*	10.2	~10.2	10.6 (5.0)
6, erythro	156	5.55	3.66	5.70	4.37	8.2	8.3	8.2	8.2	8.1 (5.2)
7b, erythro	196	5.87	3.68	5.97	4.48	*a*	2.9 (4.7)	2.8 (4.5)	2.8 (4.3)	3.1 (5.3)
Sulfone										
8, threo	118	5.70	4.46				9.9 (1.8)	10.0 (1.8)	9.8 (1.8)	10.1 (*ca.* 4.5)
9, erythro	135	6.03	4.19				2.5	2.5	2.7	3.4 (4.8)

[a] Insoluble. [b] These data are similar to those reported by D. J. Pasto, C. Cumbo, and J. Fraser, *J. Amer. Chem. Soc.*, **88**, 2194 (1966).

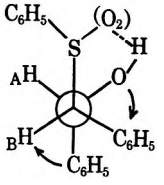
seem to make this study a special case; however, see the ensuing discussion.

The conformation of the carbon skeleton is approximated from the nmr coupling constants J_{AB}. Large values of J_{AB} (*ca.* 10–13 Hz) are taken as indicative of predominately trans protons. Small values for J_{AB} (*ca.* 1–3 Hz) reflect generally gauche protons, and intermediate values are indicative of weighted means of the above conformations.[13-15] The nmr data are recorded in Table I for **2**–**9**.

The threo sulfide **2**, J_{AB} = 8.6 Hz, preferentially occupies a conformation such as **13**, which facilitates hydrogen bonding.[16,17] The infrared hydroxyl absorption



13 (threo isomers)



14 (erythro isomers)

of **2** shows a more intense and stronger intramolecular hydrogen bonding ($\Delta\nu$ *ca.* 95 cm^{-1}) than is observed for the erythro compound **3** ($\Delta\nu$ *ca.* 35 cm^{-1}). As others have noted, deviation from a dihedral angle of 60° takes place to relieve the phenyl–phenyl interaction.[18-21] This internal rotation strengthens the hydrogen bond in the threo isomers **13** but weakens it for the erythro isomers **14**. The erythro sulfide **3**, J_{AB} ~ 6 Hz, is conformationally mixed to a larger extent than the threo isomer **2**, J_{AB} = 8.6 Hz. However, the hydroxyl resonance is a doublet for both isomers at low concentrations in deuteriochloroform. The magnitude of the H_A–C–O–H_C coupling varies with the dihedral angle[22] similar to the relationship given by Karplus.[13] For **2** the magnitude of J_{AC} (*ca.* 2 Hz) is in accord with intramolecular hydrogen bonding. The larger value observed for **3** (3.6 Hz) is consistent with considerable rotational averaging. In DMSO solutions, hydrogen bonding to solvent occurs, resulting in still larger values for J_{AC}.

Moving from the sulfides to the sulfoxides, conformer **13** becomes still more highly populated for the threo isomers. Conformer **14** is clearly predominant for *erythro*-**7** (J_{AB} = 2.9 Hz), but **6** (J_{AB} = 8.3 Hz) prefers a conformer with trans protons. This observation was unexpected since in other examples the two erythro and the two threo isomers have occupied similar conformations.[11]

In *threo*-**4** a strong intramolecular hydrogen bond is present. The hydroxyl resonance is a doublet, J_{AC} = 1.8 Hz. This resonance (δ 5.88) does not shift upfield upon dilution, unlike those of **2**, **3**, and **5**–**7**. The infrared spectrum shows a very weak "free" hydroxyl absorption at 3580 cm^{-1}, and a broad, but concentration independent, absorption at *ca.* 3350 cm^{-1}. Structure **4** then completely describes the conformation at carbon and sulfur.

The second threo isomer **5** differs from **4** in the configuration at sulfur. No hydroxyl splitting is observed in the nmr spectrum. The infrared spectrum now shows a sizable free hydroxyl absorption in addition to the broad but concentration-dependent peak at 3350 cm^{-1}. The latter persists at low concentrations, however, and is considered to be a combination of the inter- and intramolecularly bound hydroxyl absorptions.[23] The apparent molecular weight (Table II) is indicative of some external association, possibly dimerization, even at low concentrations, unlike **4** which is monomeric. This technique, however, is less sensitive to external association than spectral techniques.[24]

(13) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).
(14) R. J. Abraham and G. Gatti, *J. Chem. Soc. B*, 961 (1969).
(15) E. Garbisch, Jr., and M. Griffith, *J. Amer. Chem. Soc.*, **90**, 6543 (1968).
(16) (a) H. Szmant and J. J. Rigau, *J. Org. Chem.*, **31**, 2288 (1966); (b) R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 335 (1965).
(17) P. Schleyer and R. West, *J. Amer. Chem. Soc.*, **81**, 3164 (1959).
(18) (a) L. P. Kuhn, *ibid.*, **80**, 5950 (1958); (b) J. Sicher, M. Cherest, Y. Gault, and H. Felkin, *Collect. Czech. Chem. Commun.*, **28**, 72 (1963); (c) L. P. Kuhn, R. Schleyer, W. Baitinger, Jr., and L. Eberson, *J. Amer. Chem. Soc.*, **86**, 650 (1964).
(19) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961), and related papers.
(20) M. E. Munk, M. Meilahn, and P. Franklin, *J. Org. Chem.*, **33**, 3480 (1968).
(21) H. Bodot, J. Fediere, Guy Pozard, and L. Pujol, *Bull. Soc. Chim. Fr.*, 2260 (1968).
(22) R. R. Fraser, M. Kaufman, P. Marand, and G. Govil, *Can. J. Chem.*, **47**, 403 (1969).
(23) A. L. Ternay and D. M. Chasar, *J. Org. Chem.*, **33**, 2237 (1968).
(24) M. Davies, "Hydrogen Bonding," D. Hadzi, Ed., Pergamon Press, New York, N. Y., 1959, p 393.

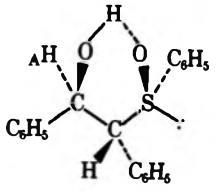
TABLE II

OSMOMETRIC APPARENT MOLECULAR WEIGHTS IN CHLOROFORM (CONCENTRATION, MG/ML)

Compd	Formula wt	Apparent molecular wt
4	322	310 (28.5),[a] 322 (0.7)
5	322	360 (10.8), 335 (0.7)
6	322	332 (14.1), 320 (0.7)
7a	322	328 (0.7)
7b	356.5	364 (5.50)
10	246	253 (25.0), 257 (12.5)
11	246	273 (25.3), 268 (17.6)

[a] Concentration in mg/ml; to convert to the same units used for the nmr studies (percentages), divide by 10.

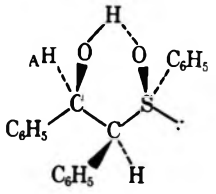
If conformer **5** were highly populated, the anisotropy of the sulfinyl group would be expected to deshield H_A by *ca.* 0.4 ppm.[23,25] On the other hand, if the alternate conformer **5′** were highly populated, H_A should be shielded by the *S*-phenyl by *ca.* 0.5 ppm.[11] The latter conformation permits hydrogen bonding but places the *S*-phenyl in a rather unfavorable conformation. Only



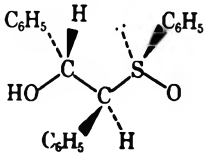
5′

a small shielding effect (0.02 ppm) is observed in comparison to the rigid structure **4** (Table I). The small change is believed to be due to population of both **5** and **5′** with cancellation of shielding and deshielding effects.

In the low-melting erythro isomer **6**, the predominant conformation prohibits both intramolecular association and dimerization. Accordingly, the infrared spectrum exhibits a strong "free" hydroxyl absorption and a relatively weak bonded hydroxyl absorption. The apparent molecular weight is close to that of the monomer. If the alternate conformation **6′** is considered, in which hydrogen bonding is possible, H_A would again be shielded by *S*-phenyl. Substantial shielding of H_A (δ



6′



6″

5.55) is indeed noted in comparison to the isomeric sulfoxide **7a** (δ 5.85). The vicinal coupling constant (J_{AB} = 8.6 Hz) is consistent with mostly **6** (or possibly **6″**), but some of the gauche H_A–H_B conformer **6′** is also present.

The fourth sulfoxide **7a** is extremely insoluble and therefore the more tractable para chloro analog **7b** was studied. The vicinal coupling constant, J_{AB} = 2.9 Hz, indicates gauche protons, and hydroxyl splitting is observed. However, the magnitude of J_{AC} (*ca.* 5 Hz)

(25) (a) R. D. Cooper P. DeMarco, N. Cheng, and N. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969); (b) C. R. Johnson and W. O. Siegl, *Tetrahedron Lett.*, 1879 (1969).

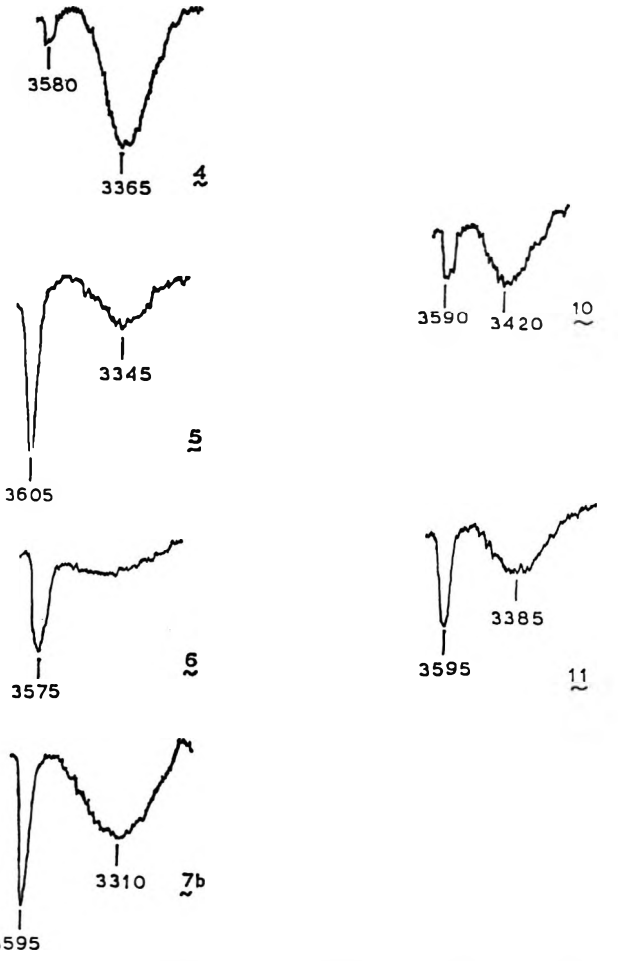


Figure 1.—The hydroxyl region of the infrared spectra of **4–7**, **10**, and **11**, taken at 0.5% concentration for **4–7**, 0.4% for **10**, and 0.44% for **11**. The solvent is deuteriochloroform.

in chloroform is almost as large as that in DMSO, where external association exists. The hydroxyl coupling constant and chemical shift are concentration dependent (Table I). The apparent molecular weight indicates some external association, even at low concentration, which suggests that dimerization may compete with intramolecular association. Any intramolecular hydrogen bond would be weakened by partial internal rotation as in structure **14**. The infrared spectrum also indicates a substantial "free" hydroxyl absorption (Figure 1).

In certain sulfoxides, Nishio has shown that the deshielding effect of trifluoroacetic acid (TFA), compared to carbon tetrachloride, was most pronounced for protons gauche to the sulfinyl oxygen and trans to the lone pair.[26] However, the four sulfoxides **4–7** were rather similar in their response to TFA compared to deuteriochloroform (Table I). In these cases, the partially protonated sulfinyl oxygen functions may occupy different conformations than the unprotonated species. Our interest in this technique was also chilled by observations on phenyl benzyl sulfoxide, which, in our hands, showed equivalent protons in either solvent.

Considering next the sulfones **8** and **9**, the J_{AB} values, 9.9 Hz and 2.5 Hz, are indicative of considerable conformational purity, on the same order as the sulfoxides **4**, **5**, and **7**. The infrared spectrum again shows

(26) (a) M. Nishio, *Chem. Commun.*, 564 (1968); (b) *ibid.*, 51 (1969). (c) For revised findings, see M. Nishio, *ibid.*, 1485 (1970).

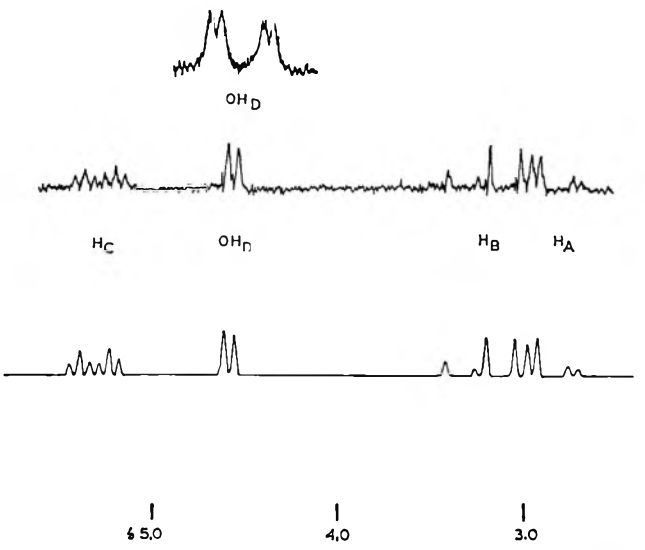


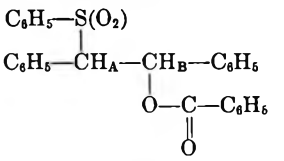
Figure 2.—Partial nmr spectrum of **11** showing the hydroxyl multiplet. The uppermost trace is a 100-Hz expansion of the hydroxyl multiplet. The lower trace is the computer simulation of the spectrum.

stronger hydrogen bonding for the threo isomer ($\Delta\nu$ 85 cm^{-1}), and hydroxyl splitting is observed for this isomer[27,28] ($\Delta\nu$ is *ca.* 45 cm^{-1} for the erythro isomer). The chemical shift of H_A of the sulfoxides **4**–**7** is rather similar to that of the sulfones **8** and **9**, but 0.5–0.9 ppm downfield from H_A of the sulfides **2** and **3**. The single sulfoxide oxygen appears to be almost as strongly deshielding as the two sulfone oxygens.[25] The general similarity of the chemical shifts of H_A in **4**–**7** suggests that the sulfinyl oxygen may be close enough in space to deshield H_A in conformers such as **1**, as well as in **1′**.

Returning to the question of the spatial requirements of the sulfinyl oxygen, sulfoxides **4** and **7** prefer the hydrogen-bonded conformation (although the bond probably is weak in **7**). The conformational preference at sulfur in *threo*-**5** is rather difficult to assess. However, it is clear that no strong preference for a hydrogen-bonded conformation exists, but whether this is due to the stability of a conformer such as **5** (in which the sulfinyl oxygen may attract H_A) or due to the instability of the hydrogen-bonded conformations is not known. The similarity of the conformation at carbon in **4** and **5** suggests that the orientation of the oxygen is not of overwhelming importance.[23,26c] With **6**, the high degree of shielding of H_A and H_B is not consistent with pure conformer **6** (or even considering an admixture of *ca.* 30% **6′**). Molecular models suggest the importance of a group of skewed conformations (one such conformation results from a partial internal rotation from **6** toward **6′**, another from **6** toward **6″**). Models suggest that H_A and H_B spend a great deal of their time over the face of the *S*-phenyl group and are thus shielded. The order of increasing general conformational purity, sulfides < sulfoxides ≤ sulfones, is similar to that usually observed upon increasing the size of one group.[29] This increase must be due to the presence of the oxygens, although the diminished C–S–phenyl angle is also a factor. The shape of the oxygens (or of the nonbonded pair at sulfur) may vary with the compound.[30–32]

In spite of the reputation of the sulfoxide group as a powerful hydrogen bond acceptor,[12,33] it is clear that this factor does not dominate the choice of conformation (*vide supra*). Thus, moving to DMSO as solvent results in a considerable change in the chemical shift (except for **4**) and coupling constant of the hydroxyl proton, which suggests that bonding to DMSO replaces intramolecular bonding. The esters of several of these compounds populate generally the same set of conformations as the parent alcohols (Table III).

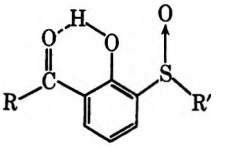
TABLE III
NMR CHEMICAL SHIFTS AND COUPLING CONSTANTS



	Chemical shifts in $CHCl_3$, ppm		Coupling constants, J_{AB} (in Hz)
	H_A	H_B	
threo-**2** OBz	4.74	6.38	7.6
erythro-**3** OBz	4.58	6.28	5.9
erythro-**7a** OBz[a]	3.98	6.98	3.3
erythro-**6a** OBz	4.02	6.76	8.7
threo-**8** OBz	4.93	6.92	10.1

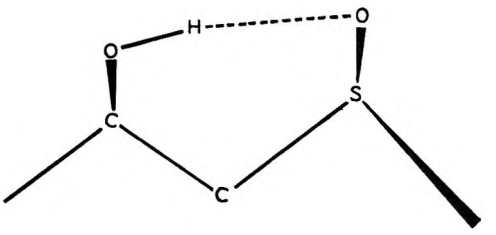
[a] The threo sulfoxide benzoates were inseparable, but coupling constants of 9.6 and 10.8 Hz were determined.

Some precedent for the weakness of the intramolecular hydrogen bond exists in the work of Chua and Hoyer,[34] who showed a preference to bonding to carbonyl over sulfoxide in **15**.



15

As the scale drawing in structure a indicates, the oxygen–oxygen distance (*ca.* 2.9 Å) is close to optimum for hydrogen bonding, and the O—H---O angle is nearly optimum, but the S—O---H angle (<90°) is very unfavorable.[21c]

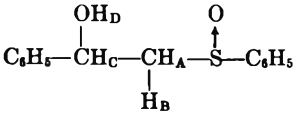


a

(27) J. P. A. Castrillon and H. H. Szmant, *J. Org. Chem.*, **32**, 976 (1967).
(28) See also W. C. Truce and T. Klinger, *ibid.*, **35**, 1834 (1970).
(29) C. A. Kingsbury and W. B. Thornton, *J. Amer. Chem. Soc.*, **88**, 3159 (1966).
(30) H. P. Koch and W. Moffitt, *Trans. Faraday Soc.*, **47**, 7 (1951).
(31) P. Haake, W. B. Miller, and D. A. Tyssee, *J. Amer. Chem. Soc.*, **86**, 3577 (1964).
(32) A. Amstutz, J. M. Hunsberger, and J. J. Chessick, *ibid.*, **23**, 1270 (1901).
(33) I. Kolthoff, M. Chantooni, and S. Bhowmik, *ibid.*, **90**, 23 (1968).
(34) M. Chua and H. Hoyer, *Z. Naturforsch., B*, 416 (1968).

TABLE IV

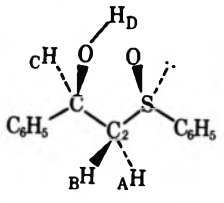
NMR CHEMICAL SHIFTS AND COUPLING CONSTANT IN 2-PHENYLSULFINYL-1-PHENYL-1-ETHANOL (10 AND 11)



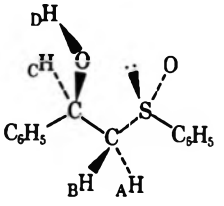
	Chemical shifts, ppm				Coupling constants, Hz				
	H_A	H_B	H_C	H_D	J_{AB}	J_{AC}	J_{BC}	J_{CD}	Other
				10% $CDCl_3$					
10	2.96	3.25	5.34	4.21	−13.2	3.3	9.6	~2.0	
11	2.79	3.21	5.30	4.58	−13.1	2.4	10.1	3.3	J_{AD} = 0.7
				5% Trifluoroacetic Acid-$CDCl_3$[b]					
10	3.41	3.95	5.36		−13.5	4.3	9.0		
11	3.51	3.55	5.49		−13.1	~1[a]	~11[a]		
				10% Benzene					
10	2.63	3.08	5.36		−12.8	3.2	9.3		
11	2.60	2.94	5.25		−12.4	2.0	10.4		

[a] Due to virtual degeneracy these coupling constants could not be determined with accuracy. [b] Equal volumes of each solvent.

In order to assess the effect of steric hindrance at C-2, the simple sulfoxides **10** and **11** were studied. The nmr data are recorded in Table IV and Figure 2. In **10**,



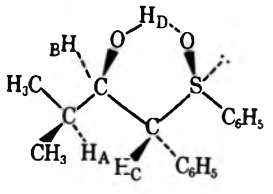
10



11

H_B is seen to be the more sensitive to TFA,[26] whereas proton H_A is the more sensitive in **11**. Both isomers show hydroxyl splitting, but that of **10** is more consistent with strong intramolecular association. The infrared spectra of both isomers show free hydroxyl absorptions at *ca.* 3595 cm^{-1} (CCl_4) but that of **10** is noticeably weaker (Figure 1). The bonded hydroxyl absorptions (*ca.* 3400 cm^{-1}) are somewhat concentration dependent but persist at low concentrations. The apparent molecular weights show **11** to be somewhat more externally associated (Table II). Thus the phenyl group at C-2 in **5**–**7** reduces external as well as some internal association, compared to **10** and **11**.

The final compound of interest, **12**, clearly is similar to **4** in its properties. The hydroxyl resonance is observed to be a triplet (Figure 3) due to equivalent three- and four-bond coupling to hydroxyl[35,36] (J_{AD} = J_{BD} = 1.6 Hz). The hydrogen bond to the sulfinyl group holds the hydroxyl group in a conformation favorable for long-range coupling, namely, the W arrangement.[35,36] The long-range coupling, J_{AD} =



12

J_{AB} = *ca.* 2Hz
J_{AD} = 1.6
J_{BC} = 10.0
J_{BD} = 1.6

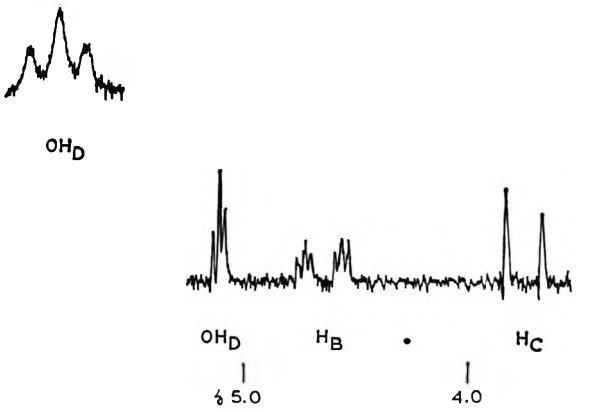


Figure 3.—Partial nmr spectrum of **12**, showing the hydroxyl triplet.

0.7 Hz, observed with **11**, is consistent with the W arrangement if a dimeric structure is postulated.

Experimental Section

The materials **2**–**9** were prepared and their configuration proven as will be reported in a later paper. The materials **10** and **11** were synthesized as follows.

To 31 g of styrene (0.298 mol) stirred in 150 ml of water plus 0.5 ml of concentrated H_2SO_4 was added 53 g of *N*-bromosuccinimide (0.241 mol) and the mixture allowed to stir overnight. The bromohydrin was taken up in 200 ml of ether, extracted several times with water, then extracted with dilute sodium bicarbonate solution, and dried ($MgSO_4$), and the solvent evaporated. The remaining oil showed the expected ABX pattern in the nmr spectrum. The oil was treated with 32.8 g of thiophenol (0.298 mol) and 16.6 g of potassium hydroxide and stirred in 150 ml of ethanol. The ethanol was evaporated by passing an air stream over the warmed solution in the hood. The remainder was taken up in ether and extracted with dilute hydrochloric acid and twice with an equal volume of water. The solution was dried ($MgSO_4$) and evaporated. Attempted vacuum distillation resulted in decomposition, and the product of another run (47 g, 0.101 mol) was oxidized directly with $NaIO_4$ (41 g, 0.191 mol). The sulfide was added to about 100 ml of methanol and the $NaIO_4$, dissolved in the minimum amount of water, was added in increments with stirring. Additional water or methanol was added from time to time to attempt to maintain a homogeneous solution. However, the precipitation of sodium iodate made this difficult. The final solution was stirred for 24 hr and filtered and extracted many times with chloroform. Each organic extract was monitored by nmr to see if additional sulfoxide was being removed from the aqueous layer. The combined chloroform layers were dried ($MgSO_4$) and evaporated, and crystallization

(35) J. C. Jochims, G. Taigel, A. Seeliger, P. Lutz, and H. Driesen, *Tetrahedron Lett.*, 4363 (1967), and later papers.

(36) C. Kingsbury, R. Egan, and T. Perun, *J. Org. Chem.* **35**, 2913 (1970).

was induced. The crude mixture of diastereomers was separated by the triangle scheme resulting in 10.4 g of **10** (mp 129.2–129.8°) and 8 g of **11** (mp 106.3–106.9°).

Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.27; H, 5.73. Found: C, 68.10; H, 5.55.

Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.27; H, 5.73. Found: C, 68.30; H, 5.72.

Compound **12** was prepared by generation of the lithium salt of phenyl benzyl sulfoxide and addition of this to isobutyraldehyde. Phenyllithium was prepared by adding 7.1 g of bromobenzene (0.046 mol) to 0.65 g of lithium stirred under nitrogen in 50 ml of ether. To this was added phenyl benzyl sulfoxide (9.0 g, 0.046 mol) dissolved in a minimum amount of tetrahydrofuran. To the resulting orange solution, isobutyraldehyde was added until the color was eliminated. The product was stirred 10 min and then added to NH_4Cl on ice. The product was taken up in warm chloroform (*ca.* 100 ml) and extracted twice with water and dried ($MgSO_4$). Separation by crystallization by the triangle scheme afforded some of two sulfoxides, mp 177–178° and 122–123°, and starting material, mp 125–126°. After a few cycles no more pure sulfoxides could be obtained. The remaining solutions were combined, concentrated, and chromatographed on a 2 × 26 cm column of Florisil.

The low-melting sulfoxide was eluted with 50% benzene in hexane yielding a total of 2.7 g from all sources. Then starting material was eluted (total of 0.9 g). Finally a mixture of sulfoxides and starting material was eluted with *ca.* 20% ether in benzene. From this more of the high-melting sulfoxide was obtained, mp 177–178° (2.2-g total). The remainder, 0.3 g, was a mixture of the high-melting sulfoxide and another sulfoxide which could not be further purified. Compound **12** melted at 122.5–123.5°.

Anal. Calcd for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.94. Found: C, 70.38; H, 7.12.

The nmr spectra were determined on a Varian A-60D instrument. The coupling constants were determined from the average of several traces of expanded spectra. In order to observe hydroxyl splittings, the chloroform solvent had to be purified by distillation from barium oxide and used soon after distillation. It was belatedly found that Linde Molecular Seive 4A would keep the solvent free from hydrochloric acid. The ABX spectra of **10** and **11** were simulated using computer techniques until the calculated trace of the spectrum was superimposible on the original. The solvent DMSO was redistilled from molecular sieve. The ir spectra were determined on a Perkin-Elmer 237 instrument standardized *vs.* polystyrene. The absorptions quoted are considered reliable to ±5 cm^{-1}. The molecular weights were determined on a Hewlett-Packard osmometer standardized *vs.* benzil, using ethanol-free chloroform as solvent. The low concentration molecular weights were determined by Dornis and Kolbe, Mülheim, West Germany. Within the context of this work, a "free" hydroxyl infrared absorption is intended to signify a hydroxyl not bonded to sulfoxide. In the ir spectra, a weak absorption at 3700 cm^{-1} was noted which was considered spurious.

Registry No.—**2**, 28520-72-1; **2** OBz, 28520-73-2; **3**, 28455-72-3; **3** OBz, 28455-73-4; **4**, 28455-74-5; **5**, 28455-94-9; **6**, 28455-75-6; **6** OBz, 28455-76-7; **7a** OBz, 28455-76-7; **7b**, 28455-78-9; **8**, 28520-74-3; **8** OBz, 28455-79-0; **9**, 28520-75-4; **10**, 28455-80-3; **11**, 28520-76-5; **12**, 28455-81-4.

Reactions of Carbanions of Dimethyl Sulfoxide and Dimethyl Sulfone with Isocyanates, Isothiocyanates, and Other Electrophilic Reagents. Preparation of β-Amido and β-Thioamido Sulfoxides and Sulfones

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Reaction of the carbanions of dimethyl sulfoxide and dimethyl sulfone with isothiocyanates gave β-thioamido sulfoxides and β-thioamido sulfones, respectively (Table I, C and E). With isocyanates, the anion of dimethyl sulfone yields methylsulfonylmalonamides (D), whereas the anion of dimethyl sulfoxide gives a mixture of β-amido sulfoxides and methylsulfinylmalonamides (A and B).

Additions of the conjugate bases of dimethyl sulfoxide or dimethyl sulfone to esters,[1,2] Schiff bases,[1] aldehydes, and ketones[3] have led to the preparation of a variety of substituted sulfoxides and sulfones. In view of the proven usefulness of these compounds in organic synthesis,[4] and of our continuing interest in new carbon to carbon bond formations,[5] we have investigated the reaction of the carbanions of dimethyl sulfoxide and dimethyl sulfone with other electrophilic reagents, such as isocyanates, isothiocyanates, nitrile, isonitrile, and benzoxazinone.

Addition of phenyl isocyanate to a solution of sodium methylsulfinylmethide gave two readily separable compounds which were assigned structures **1** and **2** (Scheme I).

The structure assignment of compound **2** was based on elemental analysis and the following physical data: ν^{Nujol} 3280 (NH), 1680 (CO), 1040 cm^{-1} (SO); λ_{max}^{EtOH} 253 mμ (ε 25,400) (nearly twice as intense as the corresponding band of **1**); δ (DMSO) singlet at 4.91 (CH), two one-proton singlets in the $CONHC_6H_5$ region (confirmed by D_2O exchange) at 9.43 and 9.69 ppm. Compound **2** was readily cleaved to malonanilide in aqueous base. Compound **1** has been previously described;[6] spectral evidence supporting its structure is given in the Experimental Section.

Attempts at directing the synthesis toward exclusive formation of **2** by the use of a large excess of isocyanate resulted in lower yields of **2**. In line with this finding was the observation that the anion of **1** was converted to **2** very slowly, even in the presence of a large excess of isocyanate. This is perhaps surprising, since step **1** → **2** appears to be irreversible, as indicated by the failure to produce some **1** by treatment of **2** with sodium hydride.

(1) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

(2) (a) H. D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963); (b) H. O. House and J. K. Larson, *ibid.*, **33**, 61 (1968).

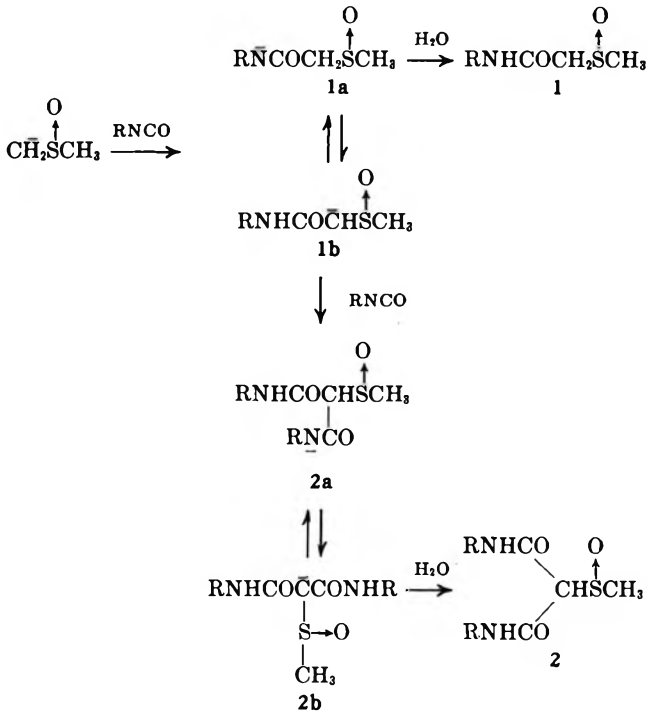
(3) (a) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962); (b) G. A. Russell and H. D. Becker, *ibid.*, **85**, 3406 (1963).

(4) G. A. Russell and L. A. Ochrymowycz *J. Org. Chem.*, **34**, 3618 (1969).

(5) (a) M. von Strandtmann, M. P. Cohen, C. Puchalski, and J. Shavel, Jr., *ibid.*, **33**, 4306 (1968); (b) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *Tetrahedron Lett.*, **35**, 3103 (1965).

(6) N. Hellstrom and T. Lauritzson, *Ber.*, **69**, 1999 (1936).

SCHEME I



Several other isocyanates employed in this reaction behaved analogously. The products are listed in Table I (types A and B).

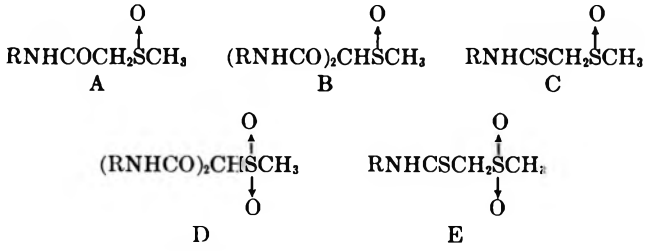


TABLE I[a]

COMPOUNDS PREPARED BY REACTIONS OF DIMETHYL SULFOXIDE OR DIMETHYL SULFONE ANIONS WITH ISOCYANATES AND ISOTHIOCYANATES

Compd	Type	R	Mp, °C	Yield, %
1	A	Phenyl	143–145	10
2	B	Phenyl	170–172	21
3	C	Phenyl	113–114	12.5
4	D	Phenyl	230–231	49
5	A	1-Naphthyl	119–121	19
6	B	1-Naphthyl	197–200	42
7	A	2-Biphenyl	97–99	17
8	B	2-Biphenyl	198–200	37
9	C	2-Naphthyl	104–105	28
10	C	Cyclohexyl	92–93	21
11	C	1-Adamantyl	165–166	59
12	E	1-Adamantyl	175–176	41

[a] Satisfactory analytical values (±0.3% for C, H, N, and S) were reported for all compounds in the table: Ed.

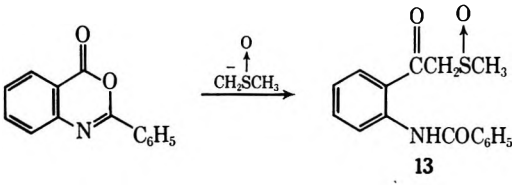
In the case of isothiocyanates the sole isolable products were the β-thioamido sulfoxides (Table I, type C). Apparently, because of the lesser electronegativity of sulfur as compared to oxygen, the methylene group of the primary product is insufficiently acidic to undergo reaction with a second mole of the isothiocyanate.

The opposite effect was observed during the reaction of phenyl isocyanate with the anion of dimethyl sulfone. In contrast to the corresponding sulfoxide, the sulfone gave only the product of double addition, β-diamido sulfone **4** (Table I, type D). In this case, the stronger electron-withdrawing effect of the sulfone group probably shifted the equilibrium extensively toward the side of the carbanion.

Compounds of Table I represent a chemical class hitherto virtually unexplored. We were able to find only one pertinent literature reference,[6] namely the preparation of compound **1** by N-acylation of aniline with thioglycolic acid followed by *S*-methylation and oxidation of the resulting *S*-methylthioglycolic anilide to the corresponding sulfoxide.

Our attempts to prepare a β-oximino sulfoxide and a β-imino sulfoxide by addition of sodium methylsulfinylmethide to 2,4,6-trimethylbenzonitrile oxide and to benzonitrile, respectively, were unsuccessful. In the case of benzonitrile, only a low yield of the corresponding β-keto sulfoxide was obtainable in crystalline form,[7] whereas the reaction with the nitrile oxide gave no isolable products under the standard conditions used in this case.

Addition of sodium methylsulfinylmethide to 2-phenyl-4-benz[4]oxazinone produced the expected 2′-[(methylsulfinyl)acetyl]benzanilide (**13**), which may be regarded as the vinylogous form of a β-amido sulfoxide.



Experimental Section[8]

I. Preparative Section. Reaction of Sodium Methylsulfinylmethide with 2-Biphenyl Isocyanate.—A mixture of 240 ml of dimethyl sulfoxide, 450 ml of benzene, and 16.5 g (0.4 mol) of 58.6% sodium hydride mineral oil dispersion was heated with stirring under nitrogen for 1 hr at 75–80°. The resulting solution was cooled to 5° and treated dropwise with a solution of 29.3 g (0.15 mol) of 2-biphenyl isocyanate in 250 ml of benzene. The addition was carried out over a period of 0.5 hr, with stirring, and ice-bath cooling to 5°. After the deep yellow solution was allowed to warm to 15–20°, 2 l. of ether was added resulting in a viscous precipitate. After decantation, trituration with ether, and decantation, *ca.* 1.5 l. of cold water followed by 0.5 l. of ether were added and the mixture was stirred vigorously. The aqueous phase was separated and acidified with 35 ml of glacial acetic acid. The separated solid was filtered and washed with *ca.* 200 ml of water and dried to give 13.0 g (37%) of *N*,*N*′-bis(2-biphenylyl)-2-(methylsulfinyl)malonamide (**8**).

The aqueous filtrate was saturated with sodium chloride and extracted with two 0.5-l. portions of ethyl acetate. The combined extracts were dried over $MgSO_4$, treated with charcoal, filtered, and evaporated under reduced pressure. The residue crystallized upon trituration with ether. It was filtered and washed with ether to give 7 g (17%) of 2-(methylsulfinyl)-2′-phenylacetanilide (**7**). All other compounds of type A and B (**1**, **2**, **5**, and **6**) were prepared by the same method. The analytical samples were obtained by recrystallization from ethyl acetate.

Reaction of Sodium Methylsulfinylmethide with Cyclohexyl Isothiocyanate.—A mixture of dimethyl sulfoxide (100 ml),

(7) After completion of of studies, G. A. Russell and L. A. Ochrymowycz (ref 4) described the preparation of β-keto sulfoxides from dimethyl sulfoxide and nitriles.

(8) Melting points were determined with the Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The authors are indebted to Dr. C. Greenough for spectral data and to Mrs. U. Zeek for elemental analyses.

benzene (300 ml), and 57% sodium hydride mineral oil dispersion (14 g, 0.33 mol) was heated at 75–80° with stirring under nitrogen until all the solid had dissolved to give a green solution (1–2 hr). Cyclohexyl isothiocyanate (21.3 g, 0.15 mol) was added over 5 min to the ice-cold solution of the dimethyl sulfoxide anion with vigorous stirring. The reaction mixture was stirred at 40° for 2 hr and poured into a large excess of ether. The white insoluble sodium salts were filtered, washed with ether, and decomposed by the addition of ice. The resulting aqueous solution was extracted with ethyl acetate. The ethyl acetate extracts were dried over sodium sulfate and evaporated to give a brown gum. The gum was triturated several times with petroleum ether (bp 30–60°) and crystallized from ethyl acetate–petroleum ether. Recrystallization from ethyl acetate gave 6.53 g (21%) of *N*-**cyclohexyl-2-(methylsulfinyl)thioacetamide** (**10**). The other compounds of type C (**3**, **9**, and **11**) were prepared by the same method.

Reaction of Sodium Methylsulfonylmethide with 1-Adamantyl Isothiocyanate.—A mixture of dimethyl sulfoxide (10 ml), 1,2-dimethoxyethane (50 ml), 57% sodium hydride mineral oil dispersion (4.2 g, 0.1 mol), and dimethyl sulfone (9.4 g, 0.1 mol) was heated at 92–95° with stirring under nitrogen for 2 hr. 1-Adamantyl isothiocyanate (10 g, 0.052 mol) in 1,2-dimethoxyethane (30 ml) was added in 2 min to the ice-cold solution of the dimethyl sulfone anion with vigorous stirring. The reaction mixture was stirred at 35° for 90 min, cooled, and poured onto ice. The white precipitate was filtered and washed with water. Two recrystallizations from methanol gave 5.96 g (41%) of pure *N*-**(1-adamantyl)-2-(methylsulfonyl)thioacetamide** (**12**).

Reaction of Sodium Methylsulfonylmethide with Phenyl Isocyanate.—A mixture of dimethyl sulfoxide (40 ml), 1,2-dimethoxyethane (200 ml), 57% sodium hydride mineral oil dispersion (16.5 g, 0.4 mol), and dimethyl sulfone (37.6 g, 0.4 mol) was heated at 80–90° with stirring under nitrogen for 3 hr. Phenyl isocyanate (24 g, 0.1 mol) in 1,2-dimethoxyethane (30 ml) was added in 2 min at 5°. The reaction mixture was stirred at 30–40° for 2 hr, cooled, and poured onto ice. The precipitate was filtered, washed with water, and dried to give *sym*-diphenylurea, 4.5 g (21%).

The aqueous filtrate was acidified with acetic acid. The white precipitate which formed was filtered, washed with water, and dried to give 16.2 g (49%) of 2-**(methylsulfonyl)**-*N*,*N*′-**diphenylmalonamide** (**4**). Recrystallization from ethanol gave an analytical sample.

Reaction of Sodium Methylsulfinylmethide with 2-Phenyl-4-oxazinone.—A mixture of dimethyl sulfoxide (25 ml), benzene (45 ml), and 57% sodium hydride mineral oil dispersion (2.5 g, 0.204 mol) was heated at 75–80° with stirring under nitrogen until all the solid had dissolved to give a green solution. 2-Phenyl-4-oxazinone (4.74 g, 0.068 mol) was added to the ice-cold solution of the dimethyl sulfoxide anion with vigorous stirring. The reaction mixture was stirred at 40° for 1 hr and poured into a large excess of ether. The yellow insoluble sodium salts were filtered, washed with ether, and dissolved in water. Acidification with acetic acid gave a white crystalline solid. Further material was obtained by extraction with ethyl acetate. Recrystallization from ethyl acetate gave pure 2-**[(methylsulfinyl)acetyl]benzanilide** as white crystals, mp 148–149°, yield 4.08 g (67%). *Anal.* Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.66; H, 5.04; N, 4.44; S, 10.88.

II. Structural and Mechanistic Studies. Reaction of Sodium Methylsulfinylmethide with Phenyl Isocyanate (Large Excess).—To the solution of 25 ml of dimethyl sulfoxide in 45 ml of benzene, 1.78 g (0.04 mol) of sodium hydride were added and the mixture was heated for 1 hr at 75°. The resulting solution was cooled to 5° and treated dropwise with a solution of 14.28 g of phenyl isocyanate in 10 ml of benzene. The reaction mixture was allowed to warm to room temperature and was worked up according to the above-described general procedure (compounds **7** and **8**). While none of **1** was detected, the yield of **2** was only 0.5 g (3.8%).

Conversion of 1 to 2.—A solution of 100 mg (0.0005 mol) of **1** in 20 ml of dimethoxyethane was treated with 24 mg (0.001 mol) of NaH and, after 2 hr of stirring, with 119 mg (0.001 mol) of phenyl isocyanate. After 60 hr of stirring at room temperature, traces of **1** were still detectable by tlc (silica gel G, ethyl acetate).

Attempt at Conversion of 2 to 1.—To the solution of 70 mg (0.0002 mol) of **2** in 5 ml of dimethoxyethane, 9.6 mg (0.0004 mole) of sodium hydride were added. After 24 hr at room temperature, tlc failed to reveal presence of **1** in the reaction mixture.

Base Cleavage of 2 to Malonanilide.—A solution of 0.8 g (0.00253 mol) of 2-(methylsulfinyl)-*N*,*N*′-diphenylmalonamide in 20 ml of 1 *N* sodium hydroxide was heated on the steam bath for 1 hr. The separated crystals were filtered, washed well with water, and dried, wt 0.5 g (77.8%), mp 225–227° (lit.[9] 225°). Recrystallization from ethyl acetate gave pure white crystals melting at 227–229°.

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.98; H, 5.62; N, 10.89.

Spectral Data of 1: ν_{max}^{Nujol} 3100–3300 (NH), 1675 (CO), 1015 cm^{-1} (SO); λ_{max}^{EtOH} 245 mμ (ε 14,250) [λ_{max}^{EtOH} for acetanilide is 242 mμ (ε 14,400)[10]]; δ (DMSO) 2.68 (CH_3), 3.81 (CH_2, quartet), 9.90 ppm (NH); mp 143–145° (lit.[6] 136–137°).

Registry No.—**1**, 29124-26-3; **2**, 29124-27-4; **3**, 29124-28-5; **4**, 29124-29-6; **5**, 29124-30-9; **6**, 29124-31-0; **7**, 29124-32-1; **8**, 29124-33-2; **9**, 29124-34-3; **10**, 29124-35-4; **11**, 29124-36-5; **12**, 29124-37-6; dimethyl sulfoxide carbanion, 13810-16-7; dimethyl sulfone carbanion, 29119-74-2; 2-[(methylsulfinyl)acetyl]benzanilide, 29124-38-7.

(9) W. Whiteley, *J. Chem. Soc.*, **83**, 34 (1903).

(10) H. E. Ungnade and R. W. Lamb, *J. Amer. Chem. Soc.*, **74**, 3789 (1954).

Substituent Effects of Positive Poles in Aromatic Substitution. IV.[1a] The Effects of Sulfonium and Selenonium Poles on the Orientation and Rate of Nitration[1b]

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The nitration of $Ph(CH_2)_nZ(CH_3)_2^+$ (where n = 0, 1, or 2 and Z = S or Se) was investigated. The rate of nitration increased, the rate of para substitution increased, and the percentage of meta substitution decreased as the positive pole was removed further from the ring and also when a sulfonium salt was compared with a corresponding selenonium salt. Relative rates were determined. Evidence of a π(d-p) interaction of the sulfonium and selenonium poles was obtained. No evidence of a π(p-p) interaction was observed.

The relative importance of resonance, inductive, and field effects of various positive poles in aromatic substitution has been reconsidered in the light of recent discoveries. The trimethylammonium group, which cannot have resonance interaction, was found to interact with the aromatic nucleus by way of the field effect rather than the inductive effect.[2] A π(p-p) resonance interaction was found to be the most influential effect of the oxonium pole which directs almost completely para in nitrations.[3] The positive poles of phosphorus, arsenic, and antimony exhibit a considerable π(d-p) overlap.[4] In the case of sulfonium and selenonium salts, a relatively strong $-I$ effect (field and/or inductive effect) should operate as it does in the previously mentioned groups. However, sulfonium and selenonium salts can have π(p-p) and π(d-p) overlap unlike the positive poles of phosphorus, arsenic, and antimony which can only have π(d-p) overlap and oxonium salts which can only have π(p-p) overlap. In an attempt to gain some insight into the relative importance of the effects in electrophilic aromatic substitution, the rates of nitration and orientation of $PhZ(CH_3)_2^+$, $PhCH_2Z(CH_3)_2^+$, and $PhCH_2CH_2Z(CH_3)_2^+$ (where Z = S or Se) were studied.

Orientation.—Nitration of dimethylsulfonium and dimethylselenonium salts was first investigated by Baker and Moffitt.[5] More recent investigation indicated that the nitration of dimethylphenylsulfonium methyl sulfate (**1**) and dimethylphenylselenonium methyl sulfate (**2**) in concentrated sulfuric acid resulted in small amounts of para and ortho substitution in addition to the major product resulting from meta substitution.[6] The nitration of dimethylbenzylsulfonium picrate (**3**) and dimethylbenzylselenonium picrate (**4**) was investigated to include isomer distribution of all monosubstituted products. In addition to this, 2-phenylethyldimethylsulfonium picrate (**5**) and 2-phenylethyldimethylselenonium picrate (**6**) were nitrated.

Analysis of the reaction mixtures resulting from the nitration of **3**, **4**, **5**, and **6** was accomplished by making the reaction mixture basic with sodium carbonate, adding an excess of potassium permanganate, heating for a limited period of time, acidifying, and extracting the nitrobenzoic acids with ether. The acids were converted to the methyl esters with diazomethane and then analyzed gas chromatographically. A known mixture of *o*-, *m*-, and *p*-nitrobenzyldimethylsulfonium salts was treated in a manner identical with the nitration procedure and analysis. Good agreement of actual and theoretical ratios of isomers was obtained provided that the time of permanganate reflux was not more than 15 min (see Experimental Section, Table V). No evidence of starting material, disubstitution, or rearrangement of isomers was obtained. In the nitration of **3** a yield of 94% of the nitrated products was calculated using gas chromatographic techniques indicating that the nitrations proceeded in good yield. Quantitative analysis of the nitration products of **5** and **6** could not be accomplished.

The distribution of isomers, given in Table I, follows the expected results. That is, the amount of meta substitution decreases and para substitution increases as the positive pole is removed further from the ring as is the case for **1** and **3** and also **2** and **4**.[2] Ortho substitution also increases as the positive pole is removed further.

TABLE I

ISOMER DISTRIBUTION OBTAINED IN NITRATION OF AROMATICS HAVING POSITIVE POLES

Compd no.	Aromatic	Ortho, %	Meta, %	Para, %
	$PhN(CH_3)_3NO_3$[a,b]		89	11
	$PhOPh_2BF_4$[a,c]			100
1	$PhS(CH_3)_2SO_4CH_3$[a,d]	3.6	90.4	6.0
2	$PhSe(CH_3)_2SO_4CH_3$[a]	2.6	91.3	6.1
	$PhCH_2N(CH_3)_3$ picrate[a,e]		88	10
3	$PhCH_2S(CH_3)_2$ picrate[a]	16.0	39.1	45.0
4	$PhCH_2Se(CH_3)_2$ picrate[a]	18.8	11.9	69.1
3	$PhCH_2S(CH_3)_2$ picrate[f]	13.4	38.0	48.6
4	$PhCH_2Se(CH_3)_2$ picrate[f]	12.5	18.0	69.5
7	$PhCH_2S(CH_3)_2ClO_4$[a]	16.6	38.8	44.6

[a] Nitrations were carried out in concentrated H_2SO_4 and concentrated HNO_3. [b] J. H. Ridd and J. H. Utley, *Proc. Chem. Soc.*, 24 (1964). [c] Reference 3. [d] Each value is an average of three nitrations. The value for each nitration is an average of five gas chromatographs. All values range from ±0.1 to ±0.6. [e] R. F. Goss, W. Hanhart, and C. K. Ingold, *J. Chem. Soc.*, 250 (1927). [f] Nitrations were carried out in fuming HNO_3.

It was found that there was essentially no difference in isomer distribution whether a picrate or a perchlorate salt was used as is indicated by the nitration of **3** and **7**. Also, very little difference in isomer distribution was

(1) (a) For part III, see H. M. Gilow, R. B. Camp, Jr., and E. C. Clifton, *J. Org. Chem.*, **33**, 230 (1968). (b) A preliminary report on part of this work has been given at the 25th Southwest Regional Meeting of the American Chemical Society, Tulsa, Okla., 1969, p 93. (c) H. M. G. and W. C. V. wish to thank the National Science Foundation College Science Improvement Program for support. (d) National Science Foundation Undergraduate Research Participant.

(2) T. A. Modro and J. H. Ridd, *J. Chem. Soc. B*, 528 (1968).

(3) N. N. Nesmayanov, T. P. Tolstaya, L. S. Isaeva, and A. V. Grid, *Dokl. Akad. Nauk SSSR*, **133**, 602 (1960).

(4) A. Gastaminza, T. A. Modro, J. H. Ridd, and J. H. P. Utley, *J. Chem. Soc. B*, 534 (1968).

(5) J. W. Baker and W. G. Moffitt, *J. Chem. Soc.*, 1722 (1930).

(6) H. M. Gilow and G. L. Walker, *J. Org. Chem.*, **32**, 2580 (1967).

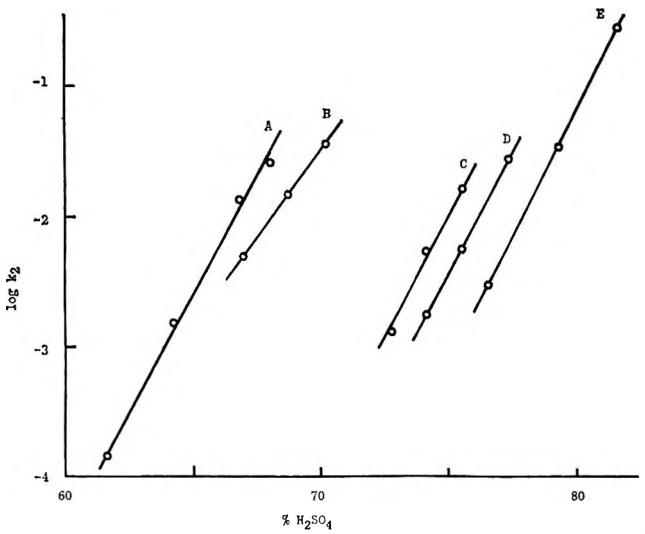

Figure 1.—Values of log k_2 *vs.* concentration of sulfuric acid: A, PhH [N. C. Deno and R. Stein, *J. Amer. Chem. Soc.*, **78**, 578 (1956)]; B, $PhCH_2CH_2S(CH_3)_2^+$ (**9**); C, $PhCH_2Se(CH_3)_2^+$ (**8**); D, $PhCH_2S(CH_3)_2^+$ (**7**); E, $PhCH_2N(CH_3)_3^+$ (ref 2).

found when concentrated sulfuric and concentrated nitric acid or fuming nitric acid was used.

Kinetics.—Equal molar concentrations of the sulfonium or selenonium salts and potassium nitrate were dissolved in a known concentration of sulfuric acid and the rate was determined. The nitration rate, which followed second-order kinetics, could be determined by following the change in concentration of nitric acid electrometrically and the organic substrate spectrophotometrically.[2] The methyl sulfate salts of the dimethylphenylsulfonium and dimethylphenylselenonium cations, **1** and **2**, and the perchlorate salts of **7**, **8**, **9**, and **10** were used in the kinetic studies so that the organic substrate would not interfere with the analysis. Second-order kinetics were followed at various concentrations of sulfuric acid for all of the substrates as is indicated in Table II.

The concentration of sulfuric acid and log k are plotted in Figure 1. The straight lines obtained for **7** and **8** have similar slopes as was obtained for benzene and some substrates with positive nitrogen poles. This permits the calculation of relative reactivities at a definite acidity as given in the last column of Table II. The relative reactivities of **1** and **2** are calculated from the fact that the nitration rates of phenyltrimethylammonium nitrate, **1** and **2**, are known at the same concentration of sulfuric acid. The plot obtained for **9** and **10** did not have a similar slope and hence the relative reactivity was not determined.

Since the rate of nitration of the phenyltrimethylammonium ion relative to that of benzene is known,[7] the data on orientation of nitration (Table I) and the relative rates of nitration (Table II) permit the calculation of partial rate factors given in Table III.

Discussion

From the relative reactivities it is clear that the dimethylsulfonium pole is a more strongly deactivating group than is the dimethylselenonium pole and that the further removed the pole is from the ring the less deactivating it becomes.[2] These results are to be expected but were not completely clarified from orientation data alone. For example, **1** and **2** have significantly different rates of nitration but form similar ratios of ortho, meta, and para nitro derivatives.

The ammonium pole is known to have such a strong $-I$ effect that meta and para substitution result.[7,8] The trimethylphenylammonium ion is 8.32 times as reactive as the dimethylphenylsulfonium ion but results in more para and less ortho substitution. If the deactivating effect of the dimethylphenylsulfonium ion were only due to a stronger $-I$ effect, considerable para and little or no ortho substitution would be expected. Since little para and some ortho substitution was observed, a $-M$ effect [π(d-p) overlap] must be important in electrophilic aromatic nitration involving the sulfonium ion. The nitro group as well as the positive poles involving phosphorus, arsenic, and antimony have been classified as $-I$ $-M$ substituents.[4] π(d-p) overlap of the sulfonium group has been established[9-13] but little has been done concerning the importance of π(d-p) overlap in aromatic substitution. It is not surprising that π(d-p) overlap, as well as the $-I$ effect, of the sulfonium group is important in electrophilic aromatic substitution.

π(p-p) overlap would result in a more reactive system and increased amounts of ortho and para substitution. The fact that the dimethylsulfonium pole deactivates the aromatic nucleus considerably and directs primarily meta suggests that π(p-p) overlap does not occur or is unimportant as compared with π(d-p) overlap.

TABLE II

RATE COEFFICIENTS FOR NITRATION IN AQUEOUS SULFURIC ACID AT 25°

Compd no.	Aromatic	H_2SO_4, %	10^3k_2 (l. mol^{-1} sec^{-1})	Relative reactivity
1	$PhS(CH_3)_2SO_4CH_3$	98.1	0.113[a]	1
2	$PhSe(CH_3)_2SO_4CH_3$	98.1	2.56	22.7
	$PhN(CH_3)_3NO_3$	98.1	0.94[b]	8.32
7	$PhCH_2S(CH_3)_2ClO_4$	77.3	2.69	1.69×10^5
7	$PhCH_2S(CH_3)_2ClO_4$	75.5	0.558	
7	$PhCH_2S(CH_3)_2ClO_4$	74.1	0.176	
8	$PhCH_2Se(CH_3)_2ClO_4$	75.5	1.62	2.46×10^5
8	$PhCH_2Se(CH_3)_2ClO_4$	74.1	0.515	
8	$PhCH_2Se(CH_3)_2ClO_4$	72.7	0.132	
	$PhCH_2N(CH_3)_3NO_3$	74.5	0.0560[c]	1.95×10^4
9	$PhCH_2CH_2S(CH_3)_2ClO_4$	70.1	3.44	
9	$PhCH_2CH_2S(CH_3)ClO_4$	68.7	1.44	
9	$PhCH_2CH_2S(CH_3)_2ClO_4$	67.0	0.488	
10	$PhCH_2CH_2Se(CH_3)_2ClO_4$	70.1	3.52	
10	$PhCH_2CH_2Se(CH_3)_2ClO_4$	68.7	1.45	
10	$PhCH_2CH_2Se(CH_3)_2ClO_4$	67.0	0.503	
	$PhCH_2CH_2N(CH_3)_3NO_3$	68.3	0.823[c]	5.50×10^7

[a] The rate coefficient was determined by following the change in concentration of nitric acid. A value of 0.120 was obtained for $PhS(CH_3)_2^+$ when the rate was followed spectrophotometrically. [b] Estimated from the rate determined in 98.7% sulfuric acid[4] assuming that the rate would change with the concentration of sulfuric acid as determined by R. J. Gillespie and D. G. Norton [*J. Chem. Soc.*, 971 (1953)]. [c] Reference 4.

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TABLE III
PARTIAL RATE FACTORS FOR NITRATION AT 25°

Compd no.	Compd	10^8 relative rate, PhH = 1	$10^8 f_o$	$10^8 f_m$	$10^8 f_p$
1	$PhS(CH_3)_2^+$	0.407	0.0440	1.10	0.147
2	$PhSe(CH_3)_2^+$	9.22	0.719	25.3	3.37
	$PhN(CH_3)_3^+$	3.39[a]		9.05[b]	2.24
7	$PhCH_2S(CH_3)_2^+$	80,000	38,400	93,800	210,000
8	$PhCH_2Se(CH_3)_2^+$	100,000	56,400	35,000	415,000
	$PhCH_2N(CH_3)_3^+$	7950[a]		20,300[b]	3980

[a] Reference 2. [b] Reference 7.

The dimethylselenonium pole is not as deactivating since the larger and less electronegative selenium would not be expected to be as good an electron withdrawer.[12] Since **2** is 22.7 times as reactive as is **1** but yields essentially the same ratio of isomers, it appears that the selenonium groups also has a π(d–p) overlap. The fact that f_m for **2** is almost three times as large as for the trimethylammonium ion but f_p is only 1.5 times as large also indicates that π(d–p) overlap is deactivating the para position more than the meta position.

Gastamiza, Modro, Ridd, and Utley[4] have pointed out that, in the cases where the $-M$ effect is important, ortho substitution may also be important suggesting that the $-M$ effect operates much more strongly on the para than on the ortho position. This is somewhat surprising since the strong $-I$ effect of positive poles strongly hinders ortho substitution. The f_o of **1** and **2** are appreciable, giving support to this approach.

When comparing the relative reactivities of the benzyl series, it is interesting to note that **7** is more reactive than is the trimethylbenzylammonium ion. It is known that the dimethylsulfonium group has a stronger $-I$ effect than the trimethylammonium group (σ_m of 1.00[8] and 0.88,[14] respectively). This suggests that **7** should be less reactive than the trimethylbenzylammonium ion; however, the opposite is true. The reactivity of **7** must be affected more by the hyperconjugative effect than is the trimethylbenzylammonium ion. The hyperconjugative effect apparently becomes more important for the sulfonium ion because the benzyl hydrogens of **7** are more acidic than the benzyl hydrogens of the ammonium ion.[15] The stronger acidity is related to the stronger electron-withdrawing effect of the sulfonium group and also the fact that the resulting ylide is stabilized by overlap with the d orbitals of sulfur.[16,17] The fact that f_o and f_p for **7** are relatively large and f_p of the trimethylbenzylammonium ion is relatively small ($f_o = 0$) also indicates that the ortho/para-directing hyperconjugative effect of **7** is important.

The overall effect of substituent groups is related to the phenyl proton nmr chemical shift. Spiesecke and Schneider[18] have found a relation between Hammett σ values and the chemical shift of para hydrogens. Figure 2 indicates the relationship of the log relative rate of nitration to the proton chemical shift. Since Hammett's values and relative rates are related, it is not surprising that the chemical shifts of sulfonium and selenonium salts are also related to the log relative rate of nitration.

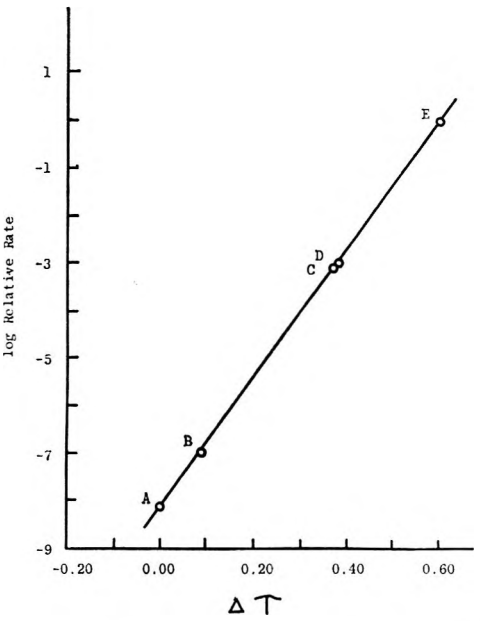

Figure 2.—The relation of the log relative rate of nitration (PhH = 1) and chemical shift difference ($\Delta\tau$) of phenyl hydrogens measured in relation to chemical shift of phenyl hydrogens of **1**: A, $PhS(CH_3)_2^+$ (**1**); B, $PhSe(CH_3)_2^+$ (**2**); C, $PhCH_2S(CH_3)_2^+$ (**7**); D, $PhCH_2Se(CH_3)_2^+$ (**8**); E, PhH.

Experimental Section

Proton nmr spectra were obtained on a Varian HA-60 spectrometer; chemical shifts are reported relative to TMS as an internal standard in CF_3CO_2H. Gas chromatographic analyses were performed on an F & M Model 700 chromatograph using a 3 ft × 1/8 in. column with 2.5% Bentone 34 and 2.5% silicone 200 on 60–80 mesh Chromosorb W DMCA/W. Ultraviolet spectra were obtained on a Beckman Model DB spectrometer. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. All melting points were determined using a Thomas-Hoover capillary melting-point apparatus. Melting points are uncorrected.

Materials.—Dimethylphenylsulfonium methyl sulfate (**1**) and dimethylphenylselenonium methyl sulfate (**2**) were prepared as described previously.[6] Dimethylbenzylsulfonium picrate (**3**) and dimethylbenzylselenonium picrate (**4**) were prepared using the method of Baker and Moffitt.[5] Picrate **3** had mp 133–134° (reported mp 134°). Picrate **4** had mp 117–118° (reported mp 118°). Perchlorates **7** and **8** were also prepared using the procedure of Baker and Moffitt except that a saturated solution of aqueous sodium perchlorate was added to the bromide salts rather than sodium picrate. After three crystallizations from 95% ethanol, a 51% yield of sulfonium salt **7** was obtained, mp 105–105.5°. *Anal.* Calcd for $C_9H_{13}ClO_4S$: C, 42.77; H, 5.18. Found: C, 42.93; H, 5.26.

After two crystallizations from 95% ethanol, a 51% yield of selenonium salt **8** was obtained, mp 91–92°. *Anal.* Calcd for $C_9H_{13}ClO_4Se$: C, 36.08; H, 4.37. Found: C, 36.27; H, 4.35.

The concentrated sulfuric acid used to carry out nitrations was reagent grade and meets ACS specifications (sp gr 1.84, 95.5–96.5%), and the concentrated nitric acid used was also reagent grade and meets ACS specifications (sp gr 1.42, 70–71%). The

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(15) W. v. E. Doering and A. K. Hoffman, *ibid.*, **77**, 521 (1955).
(16) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 71.
(17) See ref 11, p 158.
(18) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).

TABLE IV

PROTON NMR SPECTRA OF SULFONIUM AND SELENONIUM SALTS[a]

Compd no.	Compd	Phenyl protons	Methyl protons	Benzyl protons	β-Phenylethyl protons
1	$PhS(CH_3)_2^+$	2.13 (m, 5 H)	6.68 (s, 6 H)		
2	$PhSe(CH_3)_2^+$	2.22 (s, 5 H)	6.82 (s, 6 H)		
7	$PhCH_2S(CH_3)_2^+$	2.50 (s, 5 H)	7.17 (3, 6 H)	5.39 (s, 2 H)	
8	$PhCH_2Se(CH_3)_2^+$	2.51 (s, 5 H)	7.34 (s, 6 H)	5.37 (s, 2 H)	
9	$PhCH_2CH_2S(CH_3)_2^+$	2.59 (s, 5 H)	7.16 (s, 6 H)	6.67 (m,[b] 2 H)	6.28 (m,[b] 2 H)
10	$PhCH_2CH_2Se(CH_3)_2^+$	2.60 (s, 5 H)	7.40 (s, 6 H)	6.88 (m,[b] 2 H)	6.27 (m,[b] 2 H)

[a] Chemical shifts are given in τ units. The letters m and s denote multiplet and singlet, respectively. [b] An A_2B_2 pattern with a chemical shift difference of about 24 Hz.

fuming nitric acid used was 90% fuming, analytical reagent (Mallinckrodt). Solutions of sulfuric acid required as reaction media for kinetic runs were obtained by diluting concentrated sulfuric acid or adding 20% fuming sulfuric acid, analytical reagent (Mallinckrodt), and were standardized by titration of a known weight with aqueous sodium hydroxide.

2-Phenylethyldimethylsulfonium Perchlorate (9) and 2-Phenylethyldimethylsulfonium Picrate (5).—2-Phenylethyl bromide (Aldrich Chemical Co.) was added dropwise to a refluxing solution of sodium methyl thiolate similar to the procedure of Fehnel and Carmack.[19] The methyl 2-phenylethyl sulfide obtained {14.2 g, 0.039 mol, bp 78–79° (1.3 mm), $n^{25}D$ 1.5530 [reported bp 111° (12 mm), $n^{24-25}D$ 1.5494[20] and bp 111° (12 mm)[21]}} was added to 13.2 g (0.093 mol) of iodomethane and stirred overnight at room temperature. The crude solid was broken up under acetone, washed twice with acetone, and dissolved in 25 ml of water. A saturated solution of sodium perchlorate or sodium picrate was added until no more precipitate formed. After two crystallizations from 95% ethanol, the pure perchlorate **9** was obtained (15.4 g, 62% yield), mp 86–87°. *Anal.* Calcd for $C_{10}H_{15}ClO_4S$: C, 45.02; H, 5.67. Found: C, 45.01; H, 5.85.

After two crystallizations from 95% ethanol, the pure picrate **5** was obtained (20.1 g, 55% yield), mp 102–103°. *Anal.* Calcd for $C_{16}H_{17}N_3O_7S$: C, 48.60; H, 4.34. Found: C, 48.67; H, 4.55.

2-Phenylethyldimethylselenonium Perchlorate (10) and 2-Phenylethyldimethylselenonium Picrate (6).—2-Phenylethyl bromide (37.0 g, 0.20 mol) was slowly added to dimethyl selenide[22] (15.4 g, 0.14 mol) and stirred on a magnetic stirrer for about 1 month in a tightly stoppered flask. The mixture was filtered and the precipitate was thoroughly and rapidly washed with acetone and dissolved in 20 ml of water, and a saturated aqueous solution of sodium perchlorate or sodium picrate was added until no more precipitate formed. The precipitate was isolated by filtration and then crystallized twice from 95% ethanol. The perchlorate **10** was obtained in a 12% yield (5.4 g), mp 72–73° (Table IV). *Anal.* Calcd for $C_{10}H_{15}ClO_4Se$: C, 38.29; H, 4.82. Found: C, 38.13; H, 4.82.

The picrate **6** was obtained in an 11% yield (6.3 g), mp 112–113°. *Anal.* Calcd for $C_{16}H_{17}N_3O_7S$: C, 48.60; H, 4.34. Found: C, 48.76; H, 4.55.

***o*-, *m*-, and *p*-Nitrobenzylimethylsulfonium Perchlorate (11, 12, and 13).**—Perchlorates **11**, **12**, and **13** were prepared according to the procedure of Moffitt and Baker[5] except that a saturated solution of sodium perchlorate was added to an aqueous solution of the corresponding sulfonium bromides. The *o*-nitro perchlorate **11** was isolated in an 80% yield, mp 104–105°. *Anal.* Calcd for $C_9H_{12}O_6NS$: C, 36.05; H, 4.04. Found: C, 36.05; H, 4.09.

The *m*-nitro perchlorate **12** was isolated in a 71% yield, mp 122–124°. Found: C, 35.84; H, 4.14.

The *p*-nitro perchlorate **13** was isolated in an 85% yield, mp 155–156°. Found: C, 36.55; H, 3.95.

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Nitration and Analysis of Reaction Mixture.—Nitration of **1** and **2** has been previously described.[6] Picrates **3**, **4**, **5**, **6**, and perchlorate **7** were nitrated by adding 1 g of the salt to a mixture of 3 ml of concentrated sulfuric acid and 2 ml of concentrated nitric acid cooled to ice bath temperature and stirred for 15 min. The mixture was then poured on 25 g of crushed ice and made basic with solid Na_2CO_3. A saturated solution of $KMnO_4$ (200 ml) was added to the mixture, heated to reflux with stirring, and then methanol was added dropwise to destroy excess $KMnO_4$. (If reflux is continued for 15 min or longer, correct results will not be obtained.) Manganese dioxide was removed by suction filtration; the filtrate was acidified with dilute sulfuric acid and extracted with three 100-ml portions of ether. An excess of an ether solution of diazomethane (prepared from Diazald, Aldrich Chemical Co.) was added to the ether extracts and dried over anhydrous Na_2SO_4 and the ether was evaporated on a rotary evaporator. The residue was dissolved in 3 ml of chloroform and the mixture of methyl nitrobenzoates was analyzed gas chromatographically. The results are given in Table I.

A known mixture of *o*-, *m*-, and *p*-nitrobenzyldimethylsulfonium perchlorate (**11**, **12**, and **13**) was treated in a manner identical with the nitration procedure described. The results in Table V help to verify that the results obtained from gas chromatographic analysis is an accurate analysis of the reaction products. It was assumed that this analysis was also accurate for the other systems studied.

TABLE V

GAS CHROMATOGRAPHIC ANALYSIS OF A KNOWN MIXTURE OF *o*-, *m*-, AND *p*-NITROBENZYLDIMETHYLSULFONIUM PERCHLORATE

	Ortho, %	Meta, %	Para, %
Calcd	34.22	34.67	31.10
Anal.[a]	34.3	34.1	31.7

[a] Each value is an average of five gas chromatographic analyses.

Each individual nitro perchlorate **11**, **12**, and **13** was treated in a manner identical with the nitration procedure described. Only the corresponding methyl *o*-, *m*-, and *p*-nitrobenzoate was observed gas chromatographically. This indicated that there were no rearrangements occurring during the reaction or work-up.

From gas chromatographic techniques it was determined that for the nitration of picrate **3** 94% of the theoretically possible products could be accounted for. It was assumed that the other nitrations studied also gave good yields of monosubstituted products and that gas chromatographic analysis can account for more than 90% of the theoretically possible monosubstituted products. No disubstitution was observed.

Picrates **3** and **4** were also nitrated with fuming nitric acid at −8° for 1 hr. The reaction mixture was analyzed in a manner identical with the above description. Results are given in Table I.

Kinetics.—The nitrations of **1**, **7**, **8**, **9**, and **10** were started by mixing equal volumes of a sulfuric acid solution of the aromatic and KNO_3, of the same concentration, at 25.0°. Aliquot portions were withdrawn at suitable times and quenched in water, and the uv spectrum was examined. When the nitration of benzyl-

TABLE VI

NITRATION OF $PhCH_2CH_2Se(CH_3)_2ClO_4$ IN 68.7% SULFURIC ACID AT 25.0° [a]

Time, sec	0	900	1800	2700	3600	4800	6120	7200
OD (270 mμ)	0.042	0.073	0.100	0.123	0.147	0.170	0.197	0.208
$10^{-2} \times$ eq 1	0.053	0.094	0.132	0.164	0.196	0.228	0.264	0.279
k_2 l. mol^{-1} sec^{-1}		0.0138	0.0142	0.0142	0.0147	0.0145	0.0150	0.0142

[a] Initial concentration of selenonium salt and potassium nitrate = 5.96×10^{-3} *M*. Rate of nitration of **1** and **2** was also determined by analyzing the reaction mixture, at known time intervals, for nitric acid [W. D. Treadwell and H. Vontabel, *Helv. Chim. Acta*, **20**, 573 (1937)]. Reaction rates determined are given in Table II.

dimethylsulfonium perchlorate (**7**) was complete, the extinction coefficient was 8657 at 260 mμ. At 260 mμ *o*-, *m*-, and *p*-benzyldimethylsulfonium perchlorate (**11**, **12**, and **13**) had extinction coefficients of 5510, 7685, and 10,699, respectively. Assuming the ratio of isomers is the same as given in Table I, the calculated extinction coefficient for the reaction mixture is 8693 which is in good agreement with the actual value. Extinction coefficients for the other nitro isomers formed from the other aromatics were not determined, but it was assumed that the other isomers behaved similarly. There is no reason to believe that the side reactions are important since all of the extinction coefficients of the completely nitrated products were similar. The concentration of nitro compounds in the reaction mixture was determined by the method of Modro and Ridd[2] using the equation

$$x = Y_D - \epsilon_1 a/\epsilon_2 - \epsilon_1$$

where x is the combined concentration of nitrated compounds, Y is the dilution factor during quenching, D is the experimental optical density, ϵ_1 and a are the extinction coefficient of the starting material and concentration of starting material, and ϵ_2 is the extinction coefficient corresponding to a complete reaction. The value of ϵ_1, ϵ_2, and the wavelengths used for following the nitration of the sulfonium and selenonium salts were as follows: **1**, $\epsilon_1 = 783$, $\epsilon_2 = 5696$ at 256 mμ; **7**, $\epsilon_1 = 272$, $\epsilon_2 = 8657$ at 260 mμ; **8**, $\epsilon_1 = 329$, $\epsilon_2 = 9880$ at 268 mμ; **9**, $\epsilon_1 = 63$, $\epsilon_2 = 7028$ at 266 mμ; **10**, $\epsilon_1 = 47$, $\epsilon_2 = 7383$ at 270 mμ. All of the aromatics gave good agreement with the second-order kinetic equation. A typical run is shown in Table VI.

Registry No.—**1**, 6203-16-3; **2**, 13118-29-1; **3**, 29005-91-2; **4**, 29032-26-6; **5**, 29005-92-3; **6**, 29032-27-7; **7**, 18624-67-4; **8**, 29032-28-8; **9**, 29005-94-5; **10**, 29032-29-9; **11**, 29005-95-6; **12**, 29005-96-7; **13**, 29005-97-8.

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Intermediates in Nucleophilic Aromatic Substitution. X.[1,2] Kinetic and Proton Magnetic Resonance Investigations of the Interaction of Nucleophiles with 1,3,6,8-Tetranitronaphthalene

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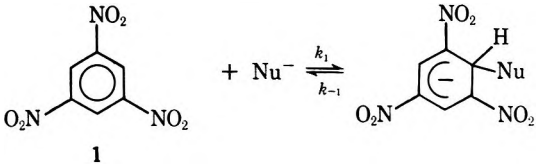
Equilibrium constants for the formation of complexes between 1,3,6,8-tetranitronaphthalene (**4**) and hydroxide and sulfite ions in water and between **4** and methoxide ions in methanol have been determined to be $(1.1 \pm 0.05)10^4$, $(1.8 \pm 0.1)10^4$, and *ca.* 10^4 l. mol^{-1}, respectively. The attainment of the equilibrium for the formation of the hydroxyl adduct of **4** (**5a**) has been followed kinetically in aqueous $Na_2B_4O_7$ buffers. The obtained data afforded rate constants for the formation (k_1) and for the decomposition (k_{-1}) of **5a**. Both k_1 and k_{-1} increase linearly with increasing buffer concentration. Solvent isotope effects of $k_1^{OH^-}/k_1^{OD^-} = 0.505$ and $k_{-1}^{OH^-}/k_{-1}^{OH^-} = 1.7$ have been determined for **5a**. Pmr investigations of the methoxyl and hydroxyl adducts of **4** have established that nucleophilic attack and rehybridization occur at C-4.

The interaction of 1,3,5-trinitrobenzene (**1**) with hydroxide,[4-6] sulfite,[6-8] and sulfide[7,8] ions in aqueous solutions as well as with alkoxide ions in alcohols[9-11] have been shown to involve the formation of Meisenheimer, or σ, complexes. Quantitative data for the equilibria



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and rate constants for these processes have become available recently.[4-11] The equilibrium constants for the formation of the corresponding complexes formed by the interaction of hydroxide ions with 1,2,3,5- (**2**) and 1,2,4,5-tetranitrobenzene (**3**)[12] afforded a comparison of the stabilities of the tri- and tetranitro-substituted cyclohexadienylide ions. Although kinetic

(1) Part IX: E. J. Fendler, D. M. Camaioni, and J. H. Fendler, *J. Org. Chem.*, **36**, 1544 (1971).

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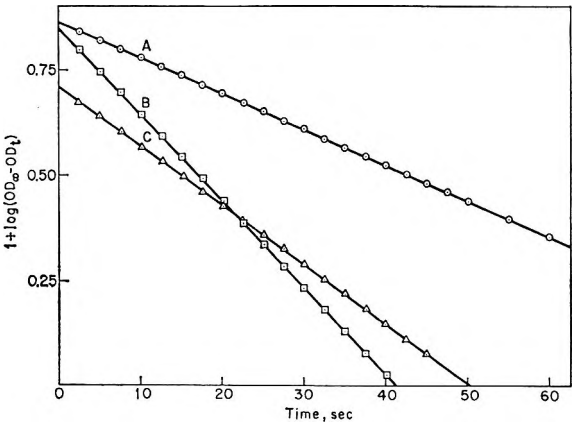


Figure 1.—Plot of log ($OD_\infty - OD_t$) against time for the attainment of equilibrium of **5a** in 2.00% dioxane at 25.00°, [**4**] = 1.25×10^{-4} *M*: A, D_2O, 1.00×10^{-2} *M* $Na_2B_4O_7$, $[OD^-] = 6.9 \times 10^{-6}$ *M*; B, H_2O, 2.00×10^{-2} *M* $Na_2B_4O_7$, $[OH^-] = 6.34 \times 10^{-6}$ *M*; C, H_2O, 3.00×10^{-2} *M* $Na_2B_4O_7$, $[OH^-] = 3.03 \times 10^{-5}$ *M*.

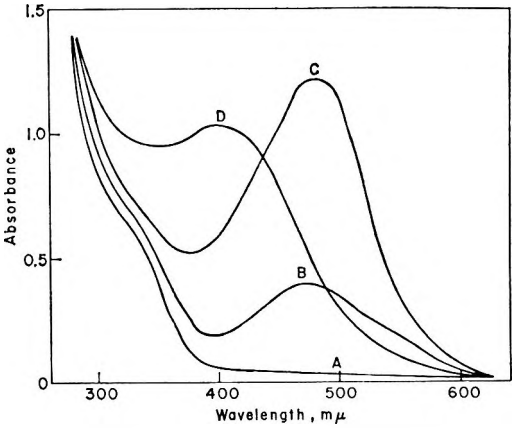


Figure 2.—Absorption spectra of **4** (1.35×10^{-4} *M*) at 25.00° using a pair of 1.00-cm matched cells: A, pH 8.02, 1.00×10^{-2} *M* $Na_2B_4O_7$; B, pH 9.06, 1.00×10^{-2} *M* $Na_2B_4O_7$; C, pH 10.00, 1.00×10^{-2} *M* Na_2HPO_4; D, 0.50 *M* NaOH.

and structural information on Meisenheimer complexes of tri- and tetranitronaphthalenes is potentially very interesting, no investigations on such systems have been carried out. We have demonstrated previously that the stabilities of the alkoxy complexes of 1-alkoxy-2,4-dinitronaphthalene were some seven orders of magnitude greater than those for the corresponding 1,1-dialkoxy-2,4-dinitrocyclohexadienylides.[13] These results were not unexpected since the resonance energy required to stabilize 1,1-dialkoxynaphthalene complexes is considerably smaller than that for the corresponding benzene complexes.[14] As part of our systematic investigations of the structures and stabilities of naphthalene Meisenheimer complexes, we report the formation of σ complexes of hydroxide, sulfite, and methoxide ions with 1,3,6,8-tetranitronaphthalene (**4**) in water and methanol. The kinetic parameters for the formation and decomposition of the hydroxide ion adduct of **4** in water and deuterium oxide as well as proton magnetic resonance parameters for both the *in situ* generated hydroxyl and methoxyl complexes of **4** are also reported.

Experimental Section

The solvents and reagents were prepared, purified, and standardized as previously described.[15] *N*,*N*-dimethylacetamide, DMA (Baker analyzed reagent grade), was stored over Linde Type 5A Molecular Sieve and its purity was verified by its pmr spectrum.

1,3,6,8-Tetranitronaphthalene (**4**) was prepared by a modified procedure of Dhar.[16] 1,8-Dinitronaphthalene (10 g, 45.8 mmol) (Aldrich Chemical Co.) was added with stirring to a solution of 50 ml of fuming nitric acid (density 1.52) and 50 ml of concentrated sulfuric acid cooled to *ca.* 20°. The mixture was heated slowly (1 hr) to 80° and at 80–90° for 3 hr. After cooling the reaction mixture to room temperature, it was filtered giving crystalline fraction A, and the filtrate was poured into ice water and filtered giving crystalline fraction B. After drying *in vacuo*, both A and B were found to be crude **4** from their pmr spectra and melting points, the former being more pure. After recrystallization of A from 95% ethanol and drying *in vacuo*, the white needles of **4** melted at 203.5–204.5° (lit.[17] mp 203°).

The pH of the buffer solutions was measured with an Orion-801 digital pH meter at 25.0°. The pD value was obtained from the relationship, pD = pH + 0.4,[18] and the concentration of OD^- ions was calculated from the ionization constant of D_2O at 25.0°,[19] *i.e.*, pOD = 14.869 − pD.

Buffered sodium sulfite solutions were prepared immediately prior to use. The absorption spectra of **4** in the different solvent systems were recorded on a Cary 14 spectrophotometer. The attainment of the equilibrium for the formation of the hydroxyl adduct of 1,3,6,8-tetranitronaphthalene (**5a**) was followed at 480 nm in the thermostated cell compartment of a Beckman DU-2 spectrophotometer. The temperature inside the cells was measured and was maintained within ±0.02°. The mixing techniques for fast reactions have been described previously.[20] Good pseudo-first-order plots were obtained for the equilibrium attainment of **5a** in all cases. Typical plots are illustrated in Figure 1. All kinetic runs were carried out in solutions containing 2.00% dioxane. Nitrite ion determinations were carried out as previously described.[1,21]

Pmr spectra (60 MHz) were obtained with a Varian Associates A-60 spectrometer at ambient probe temperature (31°). All spectra were determined on solutions in DMSO-d_6 or in DMA using tetramethylsilane (TMS) as an internal standard; chemical shifts are given on the τ scale in parts per million relative to TMS (τ 10.00 ppm) and are accurate to ±0.03 ppm. Chemical shift data were taken from spectra determined at a sweep width of 500 Hz; the reported coupling constants are the average of at least three determinations at 50-Hz sweep widths and are accurate to ±0.2 Hz.

Results

The absorption spectra of 1,3,6,8-tetranitronaphthalene (**4**) at different pH values in buffered solutions are given in Figure 2. Below pH 8 there is no appreciable absorption at wavelengths longer than 400 nm. As the hydroxide ion concentration is increased, a new absorption band with a maximum at 480 nm develops. The maximum absorbance at this wavelength remains essentially constant over a decade of hydroxide ion concentrations indicating the establishment of the equilibrium. In the concentration range of $(2\text{–}100)10^{-6}$ *M*

$$4 + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 5a$$

(13) J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 977 (1968).

(14) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, p 117.

(15) W. E. Byrne, E. J. Fendler, J. H. Fendler, and C. E. Griffin, *J. Org. Chem.*, **32**, 2506 (1967).

(16) S. N. Dhar, *J. Chem. Soc.*, **117**, 993 (1920).

(17) E. Lautemann and A. A. d'Aguiar, *Bull. Soc. Chim.*, **3**, 256 (1865).

(18) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

(19) A. K. Covington, R. A. Robinson, and R. G. Bates, *ibid.*, **70**, 3820 (1966).

(20) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, **34**, 689 (1969).

(21) We are indebted to Mr. D. M. Camaioni for these determinations.

hydroxide ion and 1.35×10^{-4} *M* **4**, it was possible to follow the equilibrium attainment of **5a** by measuring the rate of absorbance increase at 480 mm [$\epsilon_{480\ nm}$ for **5a** = $(1.8 \pm 0.2)10^4$ cm^{-1} l. mol^{-1}]. Under the experimental conditions the observed pseudo-first-order rate constant for the attainment of equilibrium, k_{obsd}, is given by

$$k_{obsd} = k_1[OH^-] + k_{-1}$$

where k_1 is the second-order rate constant for the formation of **5a** and k_{-1} is the first-order rate constant for its decomposition.[1,13,20] The pseudo-first-order rate constants at a given pH, and hence the values for k_1 and k_{-1} were found to be dependent on the concentration of the buffer. The determined rate constants, k_ψ, k_1, and k_{-1}, at 1.0, 2.0, 3.0, and 4.0 $\times 10^{-2}$ *M* buffer are given in Table I. It can be seen that both k_1 and k_{-1} increase linearly with increasing buffer concentration (Figure 3). The equilibrium constant for the formation of **5a** at zero ionic strength has been calculated to be 1.11×10^4 l. mol^{-1}. The rate constant for the sodium tetraborate catalyzed complex formation, k', is 7.46×10^3 $l.^2$ mol^{-2} sec^{-1} and that for the decomposition, $k_{-1}' = 0.23$ l. mol^{-1} sec^{-1}.

TABLE I

INTERACTION OF 1,3,6,8-TETRANITRONAPHTHALENE (1.35×10^{-4} *M*) WITH HYDROXIDE IONS IN AQUEOUS BUFFERS AT 25.00° [a]

10^2 [$Na_2B_4O_7$], *M*	10^6[OH^-], *M*	k_{obsd}, sec^{-1}	$10^{-2}k_1$, l. mol^{-1} sec^{-1} [b]	10^2k_{-1}, sec^{-1} [c]	$10^{-4}K$, l. mol^{-1} [d]
1.00	2.69	2.44	3.33	2.38	1.40
	6.33	2.58			
	8.93	2.72			
	17.8	2.94			
	43.7	3.84			
	72.6	4.56			
	85.3	5.37			
	100.0	5.70			
2.00	6.34	3.12	4.06	2.80	1.45
	10.5	3.35			
	14.2	3.45			
	21.0	3.72			
	30.0	4.15			
3.00	2.86	3.42	4.60	3.27	1.41
	6.05	3.53			
	10.2	3.71			
	15.3	3.96			
	20.5	4.20			
	27.3	4.50			
	30.3	4.68			
	34.0	4.85			
4.00	5.64	3.68	5.55	3.38	1.65
	7.69	3.83			
	10.1	3.92			
	11.3	3.99			
	14.3	4.19			
	18.3	4.42			
	24.3	4.74			
	32.3	5.20			

[a] All solutions contain 2.00% dioxane by volume. [b] Obtained from the slope of k_{obsd} *vs.* [OH^-], *M*. [c] Obtained from the intercept of k_{obsd} *vs.* [OH^-], *M*. [d] $K = k_1/k_{-1}$.

At hydroxide ion concentrations greater than 10^{-3} *M* the absorbance gradually decreases with a concomitant hypsochromic shift until it reaches 395 nm at 1.0 *M* NaOH. Further increases in the hydroxide ion concentration, up to 5.0 *M*, do not alter the absorbance or the wavelength of the absorption maximum.

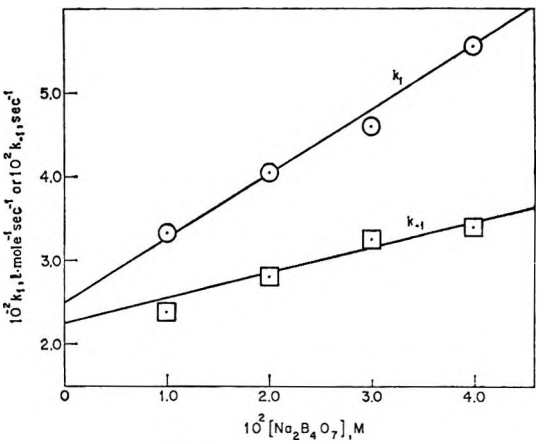


Figure 3.—Plot of k_1 (⊙) k_{-1} (⊡) *vs.* sodium tetraborate concentration.

TABLE II

INTERACTION OF 1,3,6,8-TETRANITRONAPHTHALENE (1.25×10^{-4} *M*) WITH DEUTERIOXIDE IONS AT 25.00° [a]

10^6[OD^-]	10^2k_{obsd}, sec^{-1}	$10^{-2}k$, l. mol^{-1}	10^2k_{-1}, sec^{-1}
1.99	1.58	6.60	1.40
6.90	1.94		
14.8	2.25		
21.4	3.01		
31.6	3.24		
32.4	3.52		
56.2	4.98		
100.0	8.12		

$$\frac{k_1^{OH^-}}{k_1^{OD^-}} = 0.505;^a \quad \frac{k_{-1}^{OH^-}}{k_{-1}^{OD^-}} = 1.7;^a \quad \frac{K^{OH^-}}{K^{OD^-}} = 0.298_a$$

[a] In 1.00×10^{-2} *M* $Na_2B_4O_7$ containing 1.00% dioxane by volume.

Using the obtained absolute absorbance at 480 nm for 1.0×10^{-4} *M* **4** in the pH 8.0–9.5 range ($1.0^3 \times 10^{-1}$ *M* sodium tetraborate), the equilibrium constant for the formation of **5a** has also been found to be 1.2×10^4 l. mol^{-1} from the linear Benesi–Hildebrand plot.[22]

The attainment of the equilibrium for the formation of **5a** has been measured in 1.00×10^{-2} *M* $Na_2B_4O_7$ in deuterium oxide at 25.00° (Table II). These data allowed the calculation of $k_1^{OH^-}/k_1^{OD^-} = 0.505$, $k_{-1}^{OH^-}/k_{-1}^{OD^-} = 1.70$, and $k^{OH^-}/k^{OD^-} = 0.298$.

Sulfite ions, even at concentrations of 10^{-4} *M*, produce a new absorption band centered at 480 nm in dilute solutions of **4** (Figure 4). The absorbance of the adduct showed no decomposition within 2 hr.

At higher sulfite ion concentrations the absorbance decreases and shifts to shorter wavelengths in a manner similar to that observed for **5a**. Addition of acids to these solutions resulted in absorption spectra similar to that of **4** in the aqueous buffer solution in the absence of sulfite ions. The absence of absorbance above 400 nm in acidified solutions of **4** in the presence of Na_2SO_3 is taken as evidence that SO_3^{2-} rather than HSO_3^- is the

(22) The Benesi–Hildebrand equation[23] is

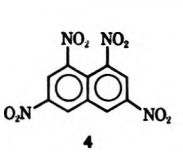
$$\frac{[4]}{A} = \frac{1}{\epsilon} + \frac{1}{K\epsilon[OH^-]}$$

where *A* is the absorbance in a 1.0-cm cell, ϵ is the molar extinction coefficient, and *K* is the equilibrium constant.

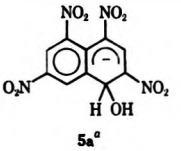
(23) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).

TABLE III

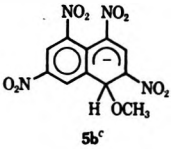
PMR PARAMETES FOR 1,3,6,8-TETRANITRONAPHTHALENE AND ITS MEISENHEIMER COMPLEXES



4



5a[a]



5b[c]

Solvent	DMSO-d_6	DMA	DMSO-d_6	DMA	DMSO-d_6	DMA
τ_2	0.08	−0.20	1.53	1.28	1.32	1.13
			1.39[b]	1.28[b]		
τ_4	0.80	0.71	4.13	3.87	4.03	3.92
			4.00[b]	3.96[b]		
τ_5	0.80	0.71	1.67	1.44	1.42	1.33
			1.50[b]	1.45[b]		
τ_7	0.08	−0.20	1.73	1.60	1.53	1.48
			1.60[b]	1.60[b]		
τ_{OCH_3}					6.92	6.82
τ_{OH}			6.19			
J_{24}	2.2	2.2	~0.6	~1.2	1.8	1.8
			~1.2[b]	~0.7[b]		
J_{45}					~0.5	~0.4
J_{57}	2.2	2.2	2.5	2.5	2.5	2.5
			2.5[b]	2.5[b]		

[a] Values were obtained for the complex generated *in situ* by the addition of 2.00 *M* aqueous KOH to *ca.* 2 *M* solutions of **4** in the indicated solvent unless specified otherwise. [b] Values were obtained using 5.00 *M* NaOH. [c] Values were obtained for the complex generated *in situ* by the addition of 5.05 *M* potassium methoxide in methanol to *ca.* 2 *M* solutions of **4** in the indicated solvent.

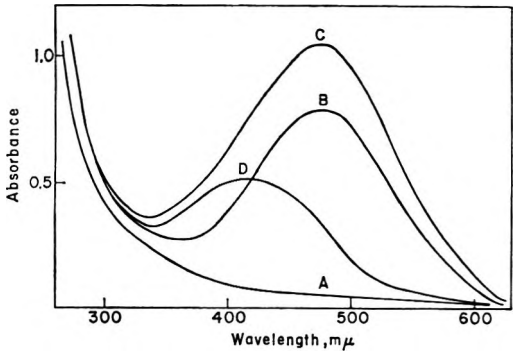


Figure 4.—Absorption spectra of **4** (6.23×10^{-5} *M*) at 25.00° using a pair of 1.00-cm matched cells: A, 1.00×10^{-2} *M* $Na_2B_4O_7$, pH 8.0; B, 1.00×10^{-4} *M* Na_2HSO_3, pH 8.0; C, 8.00×10^{-4} *M* Na_2SO_3, pH 8.00; D, 1.00 *M* Na_2SO_3, pH 8.00.

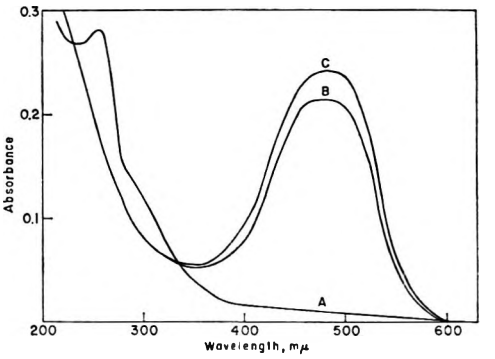


Figure 5.—Absorption spectra of **4** (1.0×10^{-5} *M*) at 25.00° using a pair of 1.00-cm matched cells: A, in methanol; B, in 5.23×10^{-4} *M* methanolic $NaOCH_3$; C, in 5.23×10^{-2} *M* methanolic $NaOCH_3$.

attacking nucleophile. The formation of the sulfite adduct of **4** is immeasurably fast by our techniques. From the absolute absorbances and the Benesi–Hildebrand equation we estimate $\epsilon_{480} = (1.8 \pm 0.8)10^4$ cm^{-1} l. mol^{-1} and $K = (2.5 \pm 1.0)10^4$ l. mol^{-1} for the formation of the sulfite adduct of **4**. The rather large errors represent the uncertainties in obtaining values for ϵ from a very small intercept in the Benesi–Hildebrand plot and errors due to the low concentrations of **4** and SO_3^{2-} required to obtain suitable absorbances.

The spectra of **4** in methanol and methanolic sodium methoxide are given in Figure 5. The formation of the methoxyl complex of **4** even at concentrations of 5×10^{-5} *M* $NaOCH_3$ and 1×10^{-5} *M* **4** is almost complete. The equilibrium constant for the formation of this complex is estimated to be $\geq 10^4$ l. mol^{-1}. At these low concentrations of reactants no quantitative determination of the equilibrium constant is feasible with the present technique.

The formation of nitrite ions is extremely slow. At 45.0° and pH 10.60, 1 equiv of nitrite ion is formed after 100 hr. Furthermore, the nitrite ion production continues, indicating the subsequent loss of additional nitro groups. Attempts to analyze the data kinetically were unsuccessful.

The pmr parameters for 1,3,6,8-tetranitronaphthalene (**4**) and its hydroxyl and methoxyl complexes **5a** and **5b** in DMSO-d_6 and DMA are given in Table III.

Discussion

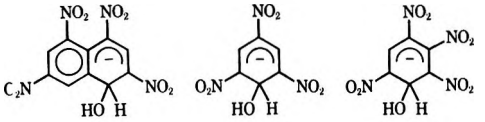
1,3,6,8-Tetranitronaphthalene (**4**) behaves analogously to 1,3,5-trinitrobenzene in that it reacts with nucleophiles such as hydroxide, sulfite, and alkoxide ions to form Meisenheimer-type complexes.[2] Quantitative data has only been obtained for the formation of the hydroxyl adduct of **4** (**5a**) and the ensuing discussion will be focused, therefore, on this complex.

The order of stability of Meisenheimer complexes parallels the extent of electron delocalization by the substituents. 1,1-Dialkoxynaphthalene Meisenheimer complexes have been found to be more stable than the corresponding cyclohexadienylides.[13,24] The equilib-

(24) J. H. Fendler and E. J. Fendler, *J. Org. Chem.*, **35**, 3378 (1970).

rium constant for the formation of the methoxyl complex of 1-methoxy-2,4-dinitronaphthalene, for example, is greater than that for the formation of 1,1-dimethoxy-2,4-dinitrocyclohexadienylide ion by a factor of 10^8.[13,25] The stability of the methoxyl complex of 1-methoxy-2,4,5-trinitronaphthalene is, on the other hand, only marginally greater than that of the 1,1-dimethoxy-2,4,6-trinitrocyclohexadienylide ion.[20,24] These results have been rationalized in terms of the proximity of the 4- and 5-nitro groups in 1-methoxy-2,4,5-trinitronaphthalene which is likely to decrease the extent of conjugation by steric hindrance.[24] The equilibrium constant for the formation of **5a** is, in fact, somewhat smaller than that for its 1,2,3,5-tetranitrobenzene analog (Table IV).

TABLE IV
KINETIC PARAMETERS FOR MEISENHEIMER COMPLEXES AT 25.00°



	5a[a]	**6a**[b]	**7**[c]
k_1, l. mol^{-1} sec^{-1}	250	37.5	
k_{-1}, sec^{-1}	2.25×10^{-1}	9.8	
K, l. mol^{-1}	1.10×10^4	3.7	2.4×10^4

[a] At zero ionic strnegth. [b] Reference 4. [c] Reference 12.

Evidence from the pmr spectra of **5a** establishes that hydroxide ion adds at the 4 position of the naphthalene. Inspection of molecular models indicates that the incoming nucleophile is sterically hindered by the peri hydrogen in the 5 position of **4** and that rehybridization of C-4 to sp^3 should result in the relief of steric strain. A comparison of the rate constants for the formation and decomposition of **5a** and the hydroxyl adduct of **1** (**6a**)[4] (k_1^{5a}/k_1^{6a} = 6.7 and k_{-1}^{6a}/k_{-1}^{5a} = 436) reveals that the greater stability of **5a** with respect to **6a** is largely due to its slower rate of decomposition. Lack of kinetic data for the formation and decomposition of the hydroxyl adduct of 2 (**7**) does not allow similar comparisons for the tetranitro-substituted benzene and naphthalene complexes. Steric effects are, of course, not the only factors which determine the stability of complexes.

Increasing concentrations of the sodium tetraborate buffer linearly enhance both k_1 and k_{-1} although the effect is considerably more pronounced for the former (Table I and Figure 3). No such effects have been noted previously for the interaction of hydroxide ions with nitro-substituted aromatics in aqueous solutions.[4,12] The kinetic parameters for the formation and decomposition of **6a** were investigated at considerably higher hydroxide ion concentrations (0.02–0.60 M) and at a constant electrolyte concentration of 1.0 M maintained by the addition of appropriate amounts of sodium chloride.[4] Unlike the case of **5a** and **6a**, the equilibrium constant for the formation of the hydroxyl adduct of 2 (**7**) was not determined kinetically by following the rate of attainment of the equilibrium but was obtained from absolute absorbance measurements of **2** in the pH 9.2–10.6 region. Unfortunately these results for the stabilities of **5a**, **6a**, and **7** are, therefore, not comparable. Pronounced ionic strength affects, however, were observed in the interaction of sulfite ions with **1**, 2,4,6-trinitroanisole, and picramide.[7] Whether the rate enhancements of k_1 and k_{-1} for **5a** represent general base catalysis, electrolyte effects, or a combination of these, their origin must be sought in terms of their differential effects on the initial and transition states for both the forward (k_1) and the reverse (k_{-1}) reactions. Indeed, Bunton and Robinson have dissected the specific salt effects on the reaction of hydroxide ion with 2,4-dinitrochlorobenzene into their component effects on the initial and transition states.[26] Both states were found to be affected by electrolytes. The rate-determining step for this reaction is the formation of the Meisenheimer-type complex, *i.e.*, k_1 in the present notation. Choosing the decomposition of a solid Meisenheimer complex, 1,1-dimethoxy-2,4,6-trinitrocyclohexadienylide ion, in water and in electrolyte solutions as a model for investigating the reverse reaction, k_{-1} in the present notation, we have observed that electrolytes, once again, influence both the initial and transition states.[27] Furthermore, their effects essentially showed a reverse trend to that observed for k_1. It is not surprising, therefore, that the overall salt effects on the equilibrium constants may, in some cases, remain unnoticed.

The magnitude of the observed deuterium solvent isotope effects, enhancement of k_1 and retardation on k_{-1} (Table II), correspond closely to those obtained for the formation and decomposition of the 1,1-dimethoxy-2-cyano-4,6-dinitrocyclohexadienylide ion ($k_1^{CH_3OH}/k_1^{CH_3OD}$ = 0.6 and $k_{-1}^{CH_3OH}/k_{-1}^{CH_3OD}$ = 1.36)[20] and its decomposition in water ($k_{-1}^{H_2O}/k_{-1}^{D_2O}$ = 1.45).[20] Solvent isotope effects of similar magnitude have been obtained for the equilibrium formation of the 1,1-dimethoxy-2,4-dinitrocyclohexadienylide ion (K^{CH_3OH}/K^{CH_3OD} = 0.38)[25] and for the ethoxy dechlorination of 2,4-dinitrochlorobenzene (k_1^{EtOH}/k_1^{EtOD} = 0.5).[28] Using the simple model of Bunton and Shiner,[29] Bernasconi has calculated the theoretical solvent isotope effect for the equilibrium formation of the dinitro-substituted Meisenheimer complexes to be K^{CH_3OH}/K^{CH_3OD} = 0.47 and interpreted the observed results as a secondary solvent isotope effect.[25] The observed solvent isotope effects on K_{5a} seem to be typical, therefore, for nucleophilic aromatic substitutions.

The structures of complexes **5a** and **5b** have been established from the pmr spectra obtained for the complexes generated *in situ* by the dropwise addition of the appropriate base (5.05 M methanolic potassium methoxide, 2.00 M aqueous potassium hydroxide, or 5.00 M aqueous sodium hydroxide) to *ca.* 2 M solutions of **4** in DMSO-d_6 or DMA. The spectrum of **4** in DMSO-d_6 consists of two doublets which, on the addition of methanolic potassium methoxide, decrease in intensity with the concurrent appearance and increase in intensity of an upfield one-proton doublet of doublets (τ 4.03), two one-proton doublets (τ 1.32 and 1.53), and a one-proton doublet of doublets at τ 1.42 (see Table III

(25) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **90**, 4982 (1968).

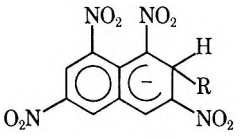
(26) C. A. Bunton and L. Robinson, *ibid.*, **90**, 5965 (1960).

(27) E. J. Fendler and J. H. Fendler, *Chem. Commun.*, 816 (1970).

(28) I. R. Bellobono, P. Beltrame, M. G. Cattania, and M. Simonetta, *Tetrahedron Lett.*, 2673 (1968).

(29) C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 3207 (1961).

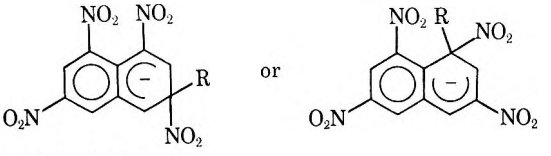
and ref 30). The chemical shifts of the methoxyl resonances in DMSO-d_6 and DMA (τ 6.92 and 6.82, respectively) are similar to those found under comparable conditions for other methoxyl Meisenheimer complexes such as that of **1** (τ 6.88), 3,5-dinitrobenzonitrile (τ 6.93), and 1,3-dicyano-5-nitrobenzene (τ 7.20),[31] in which the sp^3 carbon at the site of attack bears a proton. In addition, the chemical shifts of the upfield resonances (τ 4.03 in DMSO-d_6) attributable to a methine proton clearly indicate the formation of a σ complex, in which C-2 or C-4 has been rehybridized from sp^2 to sp^3, as opposed to a π or charge-transfer complex. The Meisenheimer, or σ, complexes of **4** could result from attack of the nucleophile at C-4 forming **5a** or **5b** or at C-2 forming **8**. However, in the case of the methoxyl com-



8, R = OCH_3 or OH

plex, the coupling of the methine proton resonance to the resonances at τ 1.32 and 1.53 in DMSO-d_6 ($J \sim$ 0.5 and 1.8 Hz) is only consistent with structure **5b** (see Table III and ref 30). It has been observed previously that the aromatic proton resonances of Meisenheimer complexes are relatively strongly shielded as compared to those of the parent aromatic compound[2,13,15,20,24] and that the magnitude of the upfield shift ($\Delta\delta$) for methoxyl Meisenheimer complexes of 1-alkoxy-2,4-dinitronaphthalenes[13] and 1-methoxy-2,4,5-trinitronaphthalene[24] reflects the relative charge densities at the various ring positions. Rehybridization of C-4 from sp^2 in **4** to sp^3 in **5a** and **5b** results in upfield shifts ($\Delta\delta$ 3.16–3.33 ppm) of the magnitude of those observed for **6a** and 1-methoxy-2,4,6-trinitrocyclohexadienylides (**6b**)[2] ($\Delta\delta$ 3.06–3.25 ppm). The H-2, H-5, and H-7 resonances also show the expected upfield shifts [H-2 ($\Delta\delta$ 1.08–1.45), H-5 ($\Delta\delta$ 0.62–0.87), and H-7 ($\Delta\delta$ 1.45–1.80 ppm)], but the magnitude of the upfield shifts of the H-7 resonance is considerably greater than that found for the sp^2 ring protons of **6a** and **6b** ($\Delta\delta$ 0.61–1.01 ppm).[2] HMO calculations of π-electron densities of 1-methoxy-2,4-dinitronaphthalene and its methoxyl complex indicate that there is a slight increase in electron density in the second ring and that the negative charge is primarily localized in the nitro groups.[32] In the case of **5a** and **5b**, the appreciable upfield shifts of the H-5 and H-7 resonances as compared to that of H-2 indicate that the negative charge is considerably delocalized in the second ring and to a greater extent than in the case of the methoxyl complex of 1-methoxy-2,4,5-trinitronaphthalene.[24] The smaller $\Delta\delta$ for H-5 is explicable in terms of anisotropic deshielding of H-5 in the complex relative to the parent naphthalene, in which peri shielding by H-4 should be greater. This effect, however, obviously is small, resulting in a decrease in the relative chemical shifts, and is insufficient to overcompensate for the increase in electron density at H-5. The observed $\Delta\delta$ values indicate a large increase in negative charge density in the second ring and localization of the charge in the nitro groups on C-6 and C-8 as well as on C-1 and C-3 and are, therefore, in qualitative agreement with the results of the HMO calculations.

In the *in situ* generation of **5a** and **5b** no pmr evidence could be obtained either for the initial or subsequent formation of a species such as **8** or for a complex in which the nucleophile is bonded to a carbon atom bearing a nitro group (**9**). At least at high concentration in



9, R = OCH_3 or OH

DMSO-d_6 and DMA, these pmr observations substantiate that a species such as **9** is a transition state rather than an intermediate in the production of nitrite ions and that the rate-determining step is its slow formation.

Registry No.—**4**, 28995-89-3; **5a**, 28984-28-3; **5b**, 28984-29-4.

Acknowledgment.—This study was supported, in part, by a grant from the U. S. Atomic Energy Commission and a portion of the pmr studies was carried out with instrumentation provided by a grant (FR-00292) from the National Institutes of Health.

(30) The 60-MHz spectra of **4** and **5b** at sweep widths of 500 Hz and of **5b** at sweep widths of 50 Hz in DMSO-d_6 will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

(31) E. J. Fendler, J. H. Fendler, C. E. Griffin, and N. L. Arthur, unpublished results.

(32) P. Caveng, P. B. Fischer, E. Heilbronner, A. L. Miller, and H. Zollinger, *Helv. Chim. Acta*, **50**, 848 (1967).

Pyrolysis Study. XX. Substituent Effects of 3-Aryl-3-buten-1-ols[1]

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The homogeneous unimolecular pyrolyses of seven 3-aryl-3-buten-1-ols have been studied in a deactivated constant-volume stainless steel reactor. Arrhenius parameters have been calculated over the temperature range 619.5–656.9°K. A value of $\rho = -0.59$ evaluated from the Hammett plot indicates modest substituent effects with little or no charge developing at the 3 position in the proposed concerted six-membered transition state. Conjugation of the olefin produced from the pyrolysis and the acidity of the alcohol hydrogen have been postulated as the major factors in controlling the rate of pyrolysis.

β-Hydroxy olefins have been reported to pyrolyze to a simpler olefin and carbonyl compounds by a unimolecular, homogeneous process, likely through a six-membered transition state.[3,4] Recently,[1] the nature of the transition state was studied using substituent effects in 1-aryl-3-buten-1-ol. Earlier Smith and Yates[5] reported the investigation of the influence of a phenyl group at the 3 and 4 positions and alkyl substituents at the 1 position on the ease of thermolysis of 3-buten-1-ol. They found that a π contribution at the 3 position increased the rate of pyrolysis, whereas it decreased the rate at the 4 position of 3-buten-1-ol. They observed the following order of reactivity, tertiary > secondary > primary alcohols, and proposed a transition state consisting of a polarized bond between C-3 and C-4 with a slight positive charge at the 3 position and a small negative charge at the 4 position. Smith and Voorhees recently reported substituent effects in the thermolysis of 1-aryl-3-buten-1-ols.[1] The present study provides quantitative information in the 3-aryl series which also supports the cyclic transition state mechanism with modest charge separation. It is particularly interesting that 1-aryl-3-buten-1-ols were shown to pyrolyze at a rate twice as fast as the most reactive previously reported β-hydroxy olefin;[5] yet the rate follows a regular Hammett $\sigma\rho$ relationship with only modest substituent effects, $\rho = -0.26$.[1]

Results

The 3-aryl-3-buten-1-ols were pyrolyzed in a deactivated stainless steel reactor[6] over a temperature range of 619.5–656.9°K, and the products, formaldehyde and a substituted α-methylstyrene, were identified by mass spectroscopy and nmr analyses, respectively. Table I summarizes the first-order rate constants, temperature, and $1/T$ for the pyrolyses. The first-order rate constants which were reproducible to ±2%, were obtained over 90% of the reaction. The stoichiometry was determined to be 1:1.95 by a ratio of P_0/P_∞.

Rates were measured under various conditions to test the unimolecularity and homogeneity of the reaction. Radical chain mechanisms were ruled out as cyclohexene, a radical inhibitor, had no effect on the rate of pyrolysis (*e.g.*, k for 3-phenyl-3-buten-1-ol was 8.60×10^{-3} with cyclohexene, compared to 8.60×10^{-3} without cyclohexene at 636.2°K). Surface catalysis for 3-phenyl-3-buten-1-ol was shown to be absent as a tenfold increase in surface to volume ratio had little effect on the rate (*e.g.*, k for 3-phenyl-3-buten-1-ol was 8.98×10^{-3} in an unpacked reactor, compared to 8.61×10^{-3} in a packed reactor at 6.36.2°K). Variation of the sample size (50–200 ml) and initial pressure (80–200 mm) was used for each compound with no effect on the rate or reproducibility between runs.

TABLE I

RATE CONSTANTS, TEMPERATURES, AND $1/T$ FOR THERMOLYSIS OF 3-ARYL-3-BUTEN-1-OLS

Compound	No. of runs	10^3k, sec^{-1}	Temp, °K	$1/T \times 10^3$
3-Phenyl-3-buten-1-ol	2	1.50	649.4	1.540
	3	1.14	641.7	1.558
	3	0.720	631.6	1.583
	2	0.411	620.1	1.613
3-*p*-Fluorophenyl-3-buten-1-ol	3	1.35	649.4	1.540
	3	0.923	640.8	1.561
	3	0.560	632.2	1.582
	3	0.502	626.3	1.597
3-*m*-Methylphenyl-3-buten-1-ol	3	1.33	646.3	1.547
	3	1.00	639.1	1.564
	3	0.749	631.9	1.582
	3	0.452	622.3	1.606
3-*p*-Methylphenyl-3-buten-1-ol	3	1.53	645.9	1.548
	3	1.15	639.2	1.564
	3	0.786	630.4	1.587
	2	0.446	619.5	1.614
3-*m*-Bromophenyl-3-buten-1-ol	3	0.822	650.1	1.538
	3	0.622	642.2	1.557
	3	0.337	631.0	1.585
	3	1.06	656.9	1.528
3-*m*-Methoxyphenyl-3-buten-1-ol	3	1.26	649.3	1.540
	3	0.887	640.6	1.561
	3	0.458	627.0	1.595
3-*p*-Chlorophenyl-3-buten-1-ol	3	1.51	653.6	1.530
	2	0.897	643.5	1.554
	2	0.620	634.8	1.575
	3	0.443	627.7	1.593

Table II is a summary of the Arrhenius parameters for the 3-aryl-3-buten-1-ols obtained by a linear regression analysis of the rate data. The correlation coefficient (> ±0.98) indicates that each compound essentially fit a straight line.

Figure 1 is a Hammett $\sigma\rho$ plot resulting in a ρ value of −0.59 calculated using a linear regression analysis.

(1) Part XIX: G. G. Smith and K. J. Voorhees, *J. Org. Chem.*, **35**, 2182 (1970).
(2) National Defense Education Act Predoctoral Fellow, 1968–1970.
(3) R. T. Arnold and G. Smolinsky, *J. Org. Chem.*, **25**, 129 (1960).
(4) G. G. Smith and R. Taylor, *Chem. Ind. (London)*, **35**, 949 (1961).
(5) G. G. Smith and B. L. Yates, *J. Chem. Soc.*, 7242 (1965).
(6) G. G. Smith and J. A. Kirby, *Analyst (London)*, **94**, 242 (1969).

TABLE II
ACTIVATION PARAMETERS FOR 3-ARYL-3-BUTEN-1-OLS

Compound	E_a, kcal	10^4k (619°K)	$\Delta S^{\ddagger}$ (619°K)	Log A	Correlation coefficient
3-Phenyl-3-buten-1-ol	35.5	3.98	−13.6	10.1	−0.999
3-*p*-Fluorophenyl-3-buten-1-ol	36.3	3.34	−12.6	10.4	−0.988
3-*m*-Methylphenyl-3-buten-1-ol	35.8	3.89	−13.2	10.2	−0.997
3-*p*-Methylphenyl-3-buten-1-ol	36.7	4.44	−11.4	10.6	−0.998
3-*m*-Methoxyphenyl-3-buten-1-ol	36.8	3.15	−11.9	10.5	−0.999
3-*m*-Bromophenyl-3-buten-1-ol	38.9	1.88	−9.5	11.0	−0.997
3-*p*-Chlorophenyl-3-buten-1-ol	38.4	2.82	−9.5	11.0	−0.999

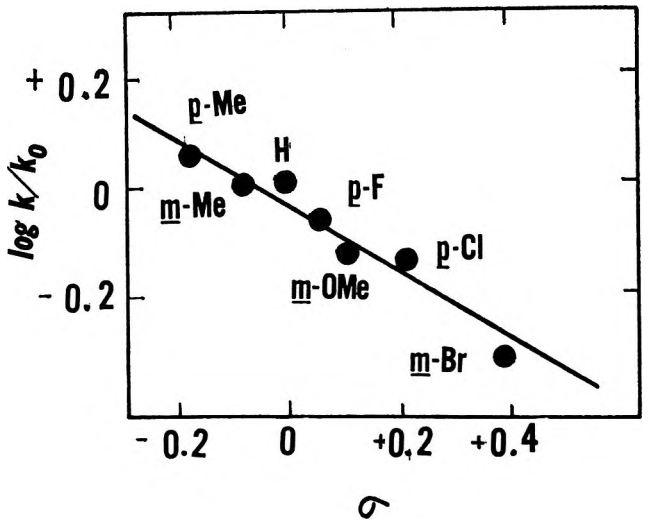

Figure 1. Hammett plot of 3-aryl-3-buten-1-ols at 619°K, ρ = −0.59.

Discussion

The results from this study on the pyrolysis of 3-aryl-3-buten-1-ols add additional evidence to substantiate the unimolecularity and homogeneity of the pyrolysis of β-hydroxy olefins; it also supports a six-membered transition state.[1,3-5,7a-c]

The activation energies reported in Table II range between 35.5 and 38.9 kcal/mol with an estimated error of ±2 kcal/mol. The $\Delta S^{\ddagger}$ values, which were calculated assuming $E_a = \Delta H^{\ddagger}$, were −9.5 to −13.6 eu. The estimated error for $\Delta S^{\ddagger}$ was ±3.0 eu.[7d] Both E_a and $\Delta S^{\ddagger}$ were in the expected range based on previously reported values[1,5] and substantiate a cyclic unimolecular process.[7d]

The calculated rate at 619°K for the thermolysis of 3-phenyl-3-buten-1-ol from data reported in this paper is 3.98×10^{-3} compared to 5×10^{-3}, the value reported earlier[5] for this compound. These rates are in reasonable agreement considering the problems associated with maintaining the temperature. The thermocouples used to measure the temperature were located in the thermostat and not directly in the reaction chamber. Although the thermocouples were frequently standardized using a National Bureau of Standards calibrated platinum resistance thermometer, a temperature gradient between the reactor and the thermostat was difficult to evaluate because of a minor but significant difference in insulation of the thermostat.

Knowing this, all substituent effect studies were referred to a standard (3-phenyl-3-buten-1-ol) run under identically the same conditions. The energy and entropy of activation for the unsubstituted 3-phenyl compound were within experimental error (above) of the values reported by Yates.

The results support only a slight charge separation in the transition state. As previously mentioned, Smith and Yates[5] postulated a slight positive charge at the 3 position. This is supported by the fact that the Hammett plot of log k/k_0 *vs.* σ for the 3-aryl-3-buten-1-ol thermolysis was linear, and the ρ was small, σ = 0.59. Furthermore a plot of Brown and Okamoto's[8] σ^+ *vs.* log k/k_0 gave more scattering of points and less statistical correlation. Even without a *p*-methoxy substituent study a curved plot was obtained when log k/k_0 was correlated with σ^+ substituent constants, particularly for the *p*-methyl substituent.

The 3 position apparently develops a slightly electron-deficient center in the transition state as noted by the size of ρ (−0.59), but the magnitude of this charge is modest. When the value of ρ is small, its sign may change with a change in temperature if the reaction is run near the isokinetic temperature.[8b] The isokinetic temperature for this reaction is 1100°K. This reaction, therefore, was carried out well below this temperature (650°) and the rate is most likely enthalpy controlled. The sign of ρ would not change over a large temperature range. Based on the comparative sizes of ρ, the magnitude of the charge at the 3 position is greater than the value of the charge at the 1 position (ρ = −0.26). Considering these two ρ values, it is of particular interest that the 1-aryl-3-buten-1-ols (Table III) have a faster rate of pyrolysis than the 3-aryl-3-buten-1-ol. Apparently, the increased rate of thermolysis by an aryl group at the 1 position cannot be explained by stabilization of the charge separation in the transition state. The 1-aryl substituent must also influence the acidity of the alcohol, along with influencing the rate.

(7) (a) R. T. Arnold and G. Smolinksy, *J. Amer. Chem. Soc.*, **82**, 4919 (1960); (b) R. T. Arnold and G. Metzger, *J. Org. Chem.*, **26**, 5185 (1961); (c) R. T. Arnold and G. Smolinsky, *J. Amer. Chem. Soc.*, **81**, 6443 (1959); (d) A. Maccoll, *Advan. Phys. Org. Chem.*, **3**, 91 (1965).

(8) (a) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958); (b) J. E. Leffler, *J. Org. Chem.*, **20**, 1210 (1955).

TABLE III
RATE CONSTANTS AND RELATVE RATES FOR THE THERMOLYSIS OF β-HYDROXY OLEFINS

Compound	10^5k, sec^{-1} (619°K)	Rel rate
4-Phenyl-3-buten-1-ol	0.012	1.0
3-Buten-1-ol	0.053	4.4
4-Penten-2-ol	0.131	10.9
2-Methyl-4-penten-2-ol	0.280	23.3
3-Phenyl-3-buten-1-ol	0.50[a]	41.5
	0.40[b]	33.2
1-Phenyl-3-buten-1-ol	1.0	83.0

[a] From ref 5. [b] From this study.

Conjugation has been noted to be especially important in gas-phase reactions[9] and has been used to explain the relative rates for the 3-phenyl- and 4-phenyl-3-buten-1-ols.[5] The sharp increase in rate of pyrolysis for the 1-aryl-3-buten-1-ols[1] seems to further exemplify the importance of conjugation in explaining the relative rates of pyrolysis for the phenyl-substituted β-hydroxy olefins. 1-Phenyl-3-buten-1-ol pyrolyzes 83 times faster than the 4-phenyl-3-buten-1-ol and almost twice as fast as the 3-phenyl-3-buten-1-ol. The products from these pyrolyses are benzaldehyde and propene from 1-phenyl, formaldehyde and 3-phenyl-propene from 4-phenyl, and formaldehyde and 2-phenylpropene from 3-phenyl-3-buten-1-ol. It is difficult to picture such a drastic change in rate unless the stabilization from conjugation of the products affects in some way the relative energy of the transition state. It also appears that the phenyl group stabilization is greater at the carbonyl position than at the olefinic position on the rate of pyrolysis. A requirement of a delicate balance between bond breaking and bond formation apparently must be present in the transition state of the thermolysis of 1- and 3-substituted 3-buten-1-ol, since data from these thermolyses follow a Hammett $\sigma\rho$ relationship appreciably better than a σ^+ relationship.

The concept of acidity of the alcohol hydrogen can also be used to explain the observed relative rates between 1-aryl- and 3-aryl-3-buten-1-ols. From the study of Smith and Yates,[5] a sequence of tertiary > secondary > primary was observed in the relative rates of thermolysis of 1-alkyl-substituted β-hydroxy olefins. This corresponds to the observed gas-phase acidity.[10] A similar comparison can be made to explain the difference in the rate of thermolysis for the 1-aryl- and 3-aryl-3-buten-1-ols. Here a comparison is being made also between a secondary and primary alcohol.

The idea of acidity fails to explain the slow rate for the 4-phenyl-3-buten-1-ol. The relative rates of thermolysis for 1-phenyl over 4-phenyl suggest that both conjugation and acidity could be operating as additive factors.

The results from this study have shown the thermolysis of β-hydroxy olefins proceeds through a highly concerted electrocyclic process with no substantial charge separation at any position. Because of the observed changes in the rate of thermolysis in chainging the position of the aryl group, it has been postulated that conjugation and the alcohol acidity are the most important factors in controlling the rate of thermolysis.

(9) A. Maccoll and P. J. Thomas, *Progr. React. Kinet.*, **4**, 119 (1967).
(10) J. I. Brauman and L. K. Blair, *J. Amer. Chem. Soc.*, **90**, 6561 (1968).

Experimental Section

Synthesis of 3-Aryl-3-buten-1-ols.—All of the 3-aryl-3-buten-1-ols were prepared using essentially the same sequence of reactions.[11,12] 3-*p*-Methylphenyl-3-buten-1-ol is given as a typical case. The synthesis of 2-*m*-bromophenylpropene is also included because of the special condition employed for dehydration. A list of yields and physical constants for the intermediates is given in Table IV, and information concerning the 3-aryl-3-buten-1-ols is given in Table V.

2-*p*-Methylphenylpropan-2-ol.—*p*-Methylacetophenone (68 g, 0.5 *M*) diluted by 100 ml of ethyl ether was added to 175 ml (0.5 *M*) of methylmagnesium bromide obtained commercially from Arapahoe Chemicals at −10° over a period of 3 hr. The mixture, which had stirred overnight, was hydrolyzed with a saturated solution of ammonium chloride. The ether layer was separated, dried with anhydrous magnesium sulfate, filtered, and evaporated. Distillation yielded 50 g of 2-*p*-methylphenylpropan-2-ol: bp 65–68° (1 mm); yield 66%; ir strong OH at 3300–3800 cm^{-1}.

2-*p*-Methylphenylpropene.—The 50 g (0.33 *M*) of 2-*p*-methylphenylpropan-2-ol was dissolved in 150 ml of acetic anhydride along with 1 g of sodium acetate and caused to reflux for 16 hr. After this period the excess acetic anhydride was hydrolyzed with a 6 *N* ammonium hydroxide solution and neutralized with a small excess of ammonium hydroxide. The solution was extracted with ether and the aqueous layer discarded. The ether solution was dried with anhydrous magnesium sulfate, filtered, and evaporated. Distillation yielded 31 g of 2-*p*-methylphenylpropene: bp 50–53° (0.65 mm); yield 73%; nmr δ 7.0 (m, aromatic), 4.9 (d, vinyl), 2.0 (s, $ArCH_3$), 1.8 (CH_2=$CArCH_3$); ir indicated hydrocarbon with terminal C=CH_2 at 1690 cm^{-1}.

3-*p*-Methylphenyl-3-buten-1-yl Acetate.—The 31 g (0.24 *M*) of 2-*p*-methylphenylpropene was added to a solution of 12.5 g (0.14 *M*) of paraformaldehyde in 150 ml of glacial acetic acid; the mixture refluxed for 3 hr; then 75 ml of acetic acid was distilled and replaced by 75 ml of acetic anhydride. The solution was neutralized with 6 *N* ammonium hydroxide solution and extracted with ether. The ether solution was dried, filtered, and evaporated. The resulting material was distilled: bp 85–94° (0.2 mm); 23 g; ir strong carbonyl band 1710 cm^{-1}, C–O band at 1030 cm^{-1}.

3-*p*-Methylphenyl-3-buten-1-ol.[9]—Hydrolysis of the 3-*p*-methylphenyl-3-buten-1-yl acetate was accomplished by refluxing 23 g (0.11 *M*) of the acetate with 5 g (0.13 *M*) of sodium hydroxide in 100 ml of 80% ethanol for 2 hr. After refluxing, the solution was cooled, washed with two 100-ml portions of water, and separated. Distillation yielded 20 g of material, bp 74–75° (0.15 mm), yield 25%, containing two products, identified from ir and nmr as 3-*p*-methylphenyl-2-buten-1-ol and 3-*p*-methylphenyl-3-buten-1-ol. Separation of 3-*p*-methylphenyl-3-buten-1-ol was accomplished (81% based on injection sample) by vpc using a 20-ft, 15% Carbowax 20M preparative column at 190° and flow rate of 26 cm^3/min: n^{25}D 1.5528; nmr δ 7.2 (m, aromatic) 5.1 (d, vinyl), 4.0 (t, CH_2CH_2OH), 3.0 (t, CH_2CH_2-OH), 2.6 (s, $ArCH_3$), 2.0 (s, CH_2OH); ir strong OH at 3400–3700 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.68; H, 8.86.

2-*m*-Bromophenylpropene.—*m*-Bromoacetophenone (75 g, 0.33 *M*) diluted with 100 ml of ethyl ether was added to 135 ml (0.33 *M*) of methylmagnesium bromide at −10° over a period of 2 hr. This mixture, which had stirred overnight, was hydrolyzed with a saturated solution of ammonium chloride. The ether layer was separated, dried, filtered, and concentrated on a rotoevaporator. The remaining organic portion was refluxed with 175 ml of acetic anhydride and 1 g of sodium acetate for 24 hr. At the end of this time the solution was hydrolyzed and neutralized with 6 *N* ammonium hydroxide solution. The solution was extracted with ether and the aqueous layer discarded. The ether layer was dried with anhydrous magnesium sulfate, filtered, and concentrated on a rotoevaporator. Distillation produced a compound, bp 110–112° (0.75 mm), that was later identified as 2-*m*-bromophenylpropan-2-yl acetate; the ir had a strong carbonyl band at 1730 cm^{-1}.

Since this method had not produced the desired substituted α-methylstyrene, the ester dissolved in 150 ml of cyclohexene

(11) C. C. Price, J. L. Benton, and C. J. Schmidle, *ibid.*, **71**, 2860 (1949).
(12) E. G. C. Hawkins and R. D. Thompson, *J. Chem. Soc.*, 370 (1961).

TABLE IV

SUMMARY OF INTERMEDIATES IN THE SYNTHESIS OF 3-ARYL-3-BUTEN-1-OLS[a,b]

		2-Aryl-2-propanol			2-Arylpropene			3-Aryl-3-buten-1-yl acetate		
Substituent	Compd no.	Registry no.	Bp, °C (mm)	Yield, g	Registry no.	Bp, °C (mm)	Yield, g	Registry no.	Bp, °C (mm)	Yield, g
H	10							7306-12-9	99–103 (0.1)	46.8
p-CH_3	11	1197-01-9	65–68 (1.0)	50	1195-32-0	50–53 (0.65)	31	29128-15-2	85–94 (0.2)	23
p-F	12	402-41-5	54–57 (0.8)	55	350-40-3	34–38 (0.7)	39.2	29128-16-3	103–109 (0.25)	29
m-CH_3	13				1124-20-5	44–46 (0.6)	52.9	29128-17-4	85–90 (0.38)	40.3
m-OCH_3	14				25108-57-0	54–56 (0.52)	30.5	29128-18-5	115–120 (0.2)	31.5
p-Cl	15	1989-25-9	70–75 (0.6)	46	1712-70-5	60–62 (0.1)	40	29128-19-6	104–110 (0.20)	16
m-Br	16				25108-58-1	63–64 (0.3)	31.1	29128-20-9	108–111 (0.53)	10.1

[a] All reagents were used in the same molar ratios as for 3-*p*-methylphenyl-3-buten-1-ol. Reflux and reaction times were also simliar. [b] Spectra were recorded for all pure intermediates and were comparable to those described for 3-*p*-methylphenyl-3-buten-1-ol.

TABLE V

PHYSICAL CONSTANTS AND YIELDS OF 3-ARYL-3-BUTEN-1-OLS

					Calcd, %		Found, %		
Compound	Registry no.	Index of refraction, $n^{25}D$	Bp, °C (mm)	Yield,[a] %	C	H	C	H	Hal
3-Phenyl-3-buten-1-ol	3174-83-2	1.5557[b]	99–101 (0.10)	37.1	81.04	8.10	81.21	8.20	
3-*p*-Methylphenyl-3-buten-1-ol	29128-22-1	1.5528	74–75 (0.15)	20.3	81.44	8.70	81.68	8.86	
3-*p*-Fluorophenyl-3-buten-1-ol	29123-91-9	1.5324	107–108 (0.25)	22.1	72.29	6.63	72.51	6.80	11.31[c]
3-*p*-Chlorophenyl-3-buten-1-ol	29123-92-0	1.5699	121 (0.45)	5.7	65.76	6.07	65.54	6.01	19.15[d]
3-*m*-Methylphenyl-3-buten-1-ol	29123-93-1	1.5503	84–86 (0.36)	21.0	81.44	8.70	81.60	8.69	
3-*m*-Bromophenyl-3-buten-1-ol	29123-94-2		123–125 (0.26)	5.5	52.86	4.85	52.98	4.86	35.49[e]
3-*m*-Methoxyphenyl-3-buten-1-ol	29123-95-3	1.5554	108–109 (0.34)	14.7	74.13	7.92	74.27	7.86	

[a] Corrected for impurity. [b] Lit.[10] $n^{25}D$ 1.5580. [c] Calcd 11.31%. [d] Calcd 19.42%. [e] Calcd 35.24%.

was passed through a Pyrex tube packed with glass tubing under nitrogen at 500°. The product was collected in a Dry Ice–isopropyl alcohol cold trap and, after distillation of the cyclohexene, 31.1 g of 2-*m*-bromophenylpropene was collected: bp 63° (0.30 mm); yield 47%; nmr δ 7.4 (m, aromatic), 5.4 (d, vinyl), 2.1 ($CH_3C{=}CH_2$); ir had a terminal double bond at 1600 cm^{-1}.

Method of Pyrolysis.—The kinetics of thermolysis were done in a deactivated stainless steel reactor[6] fitted with a null point gauge and an exterior pressure measuring system. A small sample (100–150 μl) of the alcohol was injected into the system, the reactor sealed, and the pressure change followed with time. A pressure at $t = \infty$ was determined and a plot of ln $(P_\infty - P_t)$ *vs.* time, where P_t is the pressure at time t, was used to obtain the first-order rate constants. The temperature of the pyrolysis thermostat was measured to ±0.1° by two chromel-alumel thermocouples, previously standardized against a National Bureau of Standards calibrated platinum resistance thermometer linked in series with an ice bath.

Product Analysis.—The pyrolysis products from three or four 0.3-ml injections were collected in a Dry Ice–isopropyl alcohol trap attached in the vacuum line directly behind the exhaust valve on the reactor. To ensure that all products were retained in the trap, the trap was kept at −78° until the gaseous material was distilled. Since the products from the pyrolysis of 3-aryl-3-buten-1-ol are formaldehyde and 2-arylpropene, it was necessary to distil the formaldehyde directly into a mass spectrometer gas cell and analyze directly by mass spectroscopy. The 2-arylpropenes were dissolved in Silinar C for nmr analysis.

Acknowledgment.—We wish to thank the National Defense Education Act, the National Science Foundation, Grant GP 9251, and the Utah State University Research Council for generous support of this work. We also thank Mr. J. D. Evans for his assistance in purification of the compounds used in this study. Grateful acknowledgment is also given to Murray Elevators of Salt Lake City for a small award to one of us (K. J. V.).

The Dimerization of 2-Vinylindoles and Their Alcohol Precursors[1]

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Received December 3, 1970

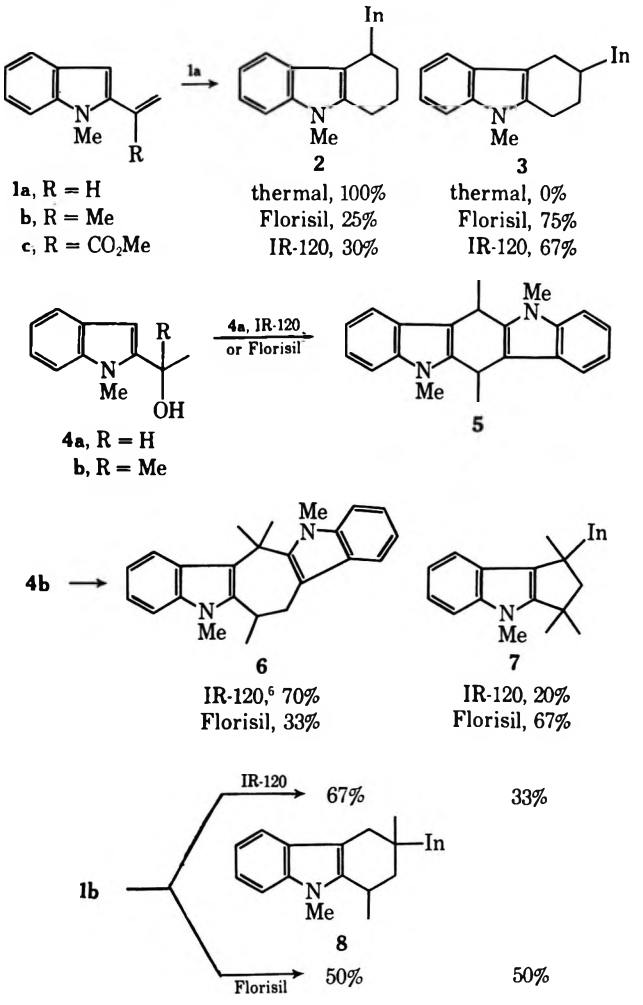
The dimerization of a select pair of 2-vinylindoles and 2-(α-hydroxyalkyl)indoles was investigated. The structures of the dimeric species are elucidated.

Since 2- and 4-vinylpyridines are well known[3] to function as electrophilic olefins, the corresponding reaction with 2-vinylindoles might be expected to behave in a similar fashion under the influence of acid catalysis. Prior to our utilization of 1-methyl-2-(α-carbomethoxyvinyl)indole (**1c**) in alkaloid synthesis,[4] we had occasion to explore the reactivity of four indolic compounds which were devoid of electron-withdrawing groups, *i.e.*, carbomethoxyl. The dimers formed from 1-methyl-2-vinylindole (**1a**), 1-methyl-2-isopropenylindole (**1b**), 1-methyl-2-(α-hydroxyethyl)indole (**4a**), and 1-methyl-2-(α-hydroxyisopropyl)indole (**4b**) under either acid and/or thermal conditions are outlined in Scheme I.[5,6]

Attempted distillation of 1-methyl-2-vinylindole (**1a**), prepared from 1-methyl-2-formylindole[7] and methylene triphenylphosphine, produced a viscous oil from which could be isolated dimer **2**. A more efficient means of effecting this transformation was achieved by refluxing the vinylindole in toluene for 30 hr. The structural assignment was made on the basis of the similarity in chemical shift and multiplicity of the high-field portion of its nuclear magnetic resonance spectrum with that of the thermal dimers of 2-vinylfuran,[8] 2-vinylthiophene,[9] and styrene.[10] The mass spectrum provided confirmatory evidence for this assignment since a metastable peak[11] at *m/e* 260.5 ($286^2/314$) can be derived from the daughter ion (*m/e* 286) and the molecular ion (*m/e* 314). The alternate assignment **3** (*vide infra*) would have been expected to yield a metastable at *m/e* 78.5 ($157^2/314$) (Scheme II).

Exposure of vinylindole **1a** in benzene solution to Florisil[12] overnight promoted self-condensation. Under these conditions, dimers **2** and **3** were obtained in a 1:3 ratio, respectively. The assignment of structure **3** to the major component followed from both its nuclear magnetic resonance spectrum and mass spectrum, the latter displaying the second fragmentation pattern[13] in

SCHEME I[5]



Scheme II. When the experiment was conducted in the absence of Florisil, only recovered starting material was obtained, indicating the reaction to be catalyzed by Florisil. Consequently, the appearance of **2** in the thermal reaction presumably arises *via* a radical pathway,[8-10] whereas dimers **2** and **3** are formed by an ionic route in the presence of Florisil.

A similar ratio of products was obtained by refluxing an ethanol solution of the vinylindole **1a** in the presence of Amberlite IR-120 sulfonic acid resin. The possibility of the reversible formation of dimers **2** and **3** was eliminated when either dimer was recovered unchanged when subjected to the conditions of IR-120 resin or Florisil.

When an attempt was made to prepare vinylindole **1a** by the dehydration of alcohol **4a**, the sole product of undefined stereochemistry was dimer **5**.

These data reflect the propensity of vinylindole **1a** to give rise to its 3-protonated species **9** as a reactive intermediate, whereas the alcohol produces the cation

(1) Taken in part from the Ph.D. thesis of E. B. S., Yale University, 1970.

(2) National Institutes of Health Predoctoral Fellow, 1966–1969.

(3) W. v. E. Doering and R. A. N. Weil, *J. Amer. Chem. Soc.*, **69**, 2641 (1947); G. Singerman and S. Danishefsky, *Tetrahedron Lett.*, 2249 (1964).

(4) F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3492 (1970).

(5) Percentages indicated represent relative amounts of products present in the crude reaction mixture as determined by the nuclear magnetic resonance spectrum. Throughout the text, In = 2-(1-methylindolyl).

(6) The mixture of the IR-120 resin and Florisil contained 10% of vinylindole **1b**.

(7) K. Hoffman, A. Rossi, and J. Kebrle, German Patent 1,093,365 (1958); *Chem. Abstr.*, **56**, 4735*f* (1962).

(8) C. A. Aso, T. Kunitake, and Y. Yanaka, *Bull. Chem. Soc. Jap.*, **38**, 675 (1965).

(9) C. A. Aso, T. Kunitake, M. Shinsenji, and H. Miyakazi, *J. Polym. Sci., Part A-1*, **7**, 1497 (1969).

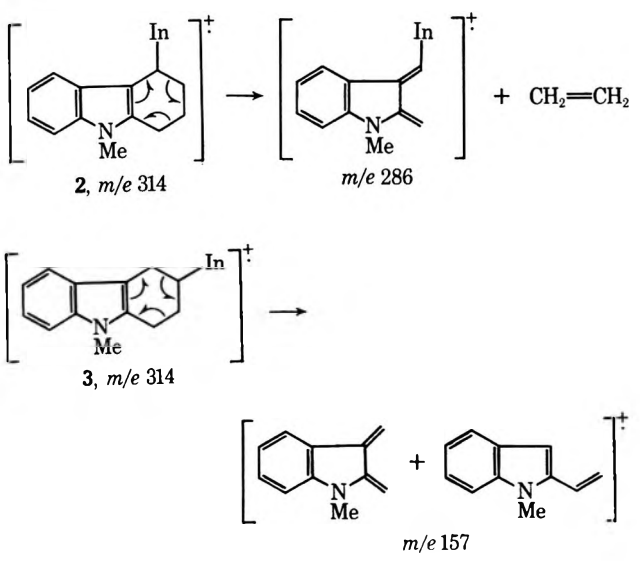
(10) F. R. Mayo, *J. Amer. Chem. Soc.*, **90**, 1289 (1968).

(11) For a discussion of metastable peaks, see K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962.

(12) Florisil is a magnesium silicate chromatographic adsorbent available from Fisher Scientific Co.

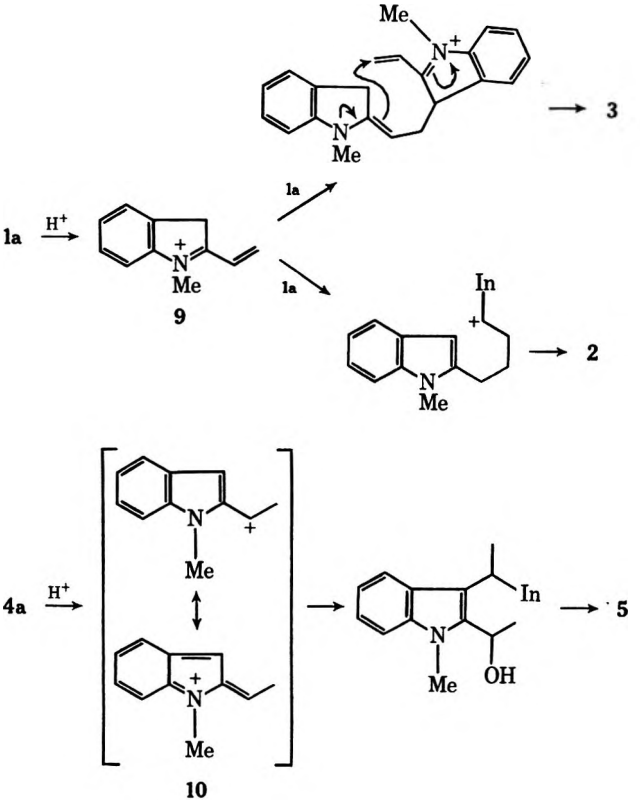
(13) Although the peak, *m/e* 157, can be attributed to a doubly charged species derived from the molecular ion, at least some of the peak must be due to fragments in light of the metastable peak.

SCHEME II



10^{14} (2-β protonated **1a**) which leads to its discrete product (Scheme III).

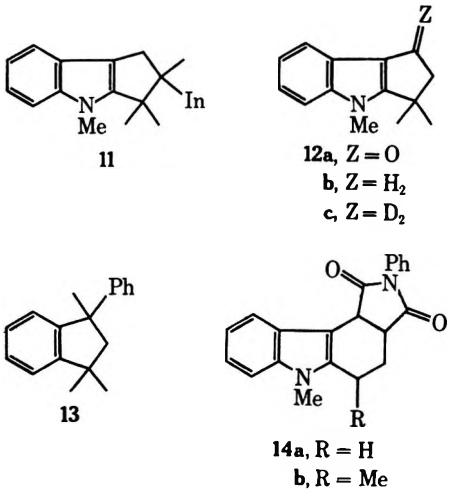
SCHEME III



In contrast to the thermal instability of 1-methyl-2-vinylindole, 1-methyl-2-isopropenylindole was capable of distillation. In addition, it was stable in refluxing ethylene glycol and could be chromatographed on Florisil. However, prolonged exposure of a benzene solution of vinylindole **1b** to Florisil provided a 1:1 mixture of dimers **7** and **8**. The structure of **8**, a single diastereomer, was dictated by its nuclear magnetic resonance spectrum which showed an AB pattern consisting of a one-proton doublet at δ 2.77 (J = 14 Hz), discernible in a three-proton signal (δ 2.50–3.00), and a partly hidden one-proton doublet at δ 3.54 (J = 14 Hz). Irradiation of either member of the AB pattern caused the other to collapse to a singlet. In addition, irradiation of the high-field side of the multiplet at δ 2.50–3.00 containing the C-1 proton and one of the C-2 protons caused collapse of a three-proton methyl doublet at δ 1.34 and a one-proton doublet of doublets centered at δ 1.78 to singlets. This clearly ruled out the possibility of the alternate mode of dimerization having the quaternary methyl and indole moiety at C-4.

The mass spectrometric fragmentation of dimer **8** was reminiscent of dimer **3** in that the parent ion m/e 342 gave rise to a base daughter peak m/e 171 in conjunction with the accompanying metastable peak at m/e 85.5 ($171^2/342$).

The second dimer revealed five three-proton singlets at δ 1.38, 1.49, 1.88, 3.57, and 3.65, an AB quartet, the halves centered at δ 2.55 and 2.90 (J = 13 Hz), and a one-proton singlet at δ 6.23 as the most salient features of its nuclear magnetic resonance spectrum. A ready distinction between structures **7** and **11** could not be made without knowing the chemical shifts of the AB quartets of at least one of these structural types. To this end, indole **12a** was prepared by the reaction of



α-methylphenylhydrazine and methyl 3,3-dimethyllevulinate in the presence of polyphosphoric acid,[15] effecting indolization and cycloacylation in one operation. Hydrogenolysis with lithium aluminum hydride–aluminum chloride[16] provided indole **12b** (m/e 199) whose nuclear magnetic resonance spectrum displayed the vicinal methylene protons as a centrosymmetric A_2B_2 multiplet with the halves centered at δ 2.31 and 2.88. When the reduction was effected with lithium aluminum deuteride–aluminum chloride, the dideuterated species **12c** (m/e 201) was produced which showed a broad two-proton singlet at δ 2.31 confirming that the high-field portion of the A_2B_2 pattern could be assigned to the homobenzylic methylene. These values are in accord with the assignment of structure **7** to this dimer. An identical substitution pattern is observed in the dimer **13** obtained from the acid-catalyzed dimerization of

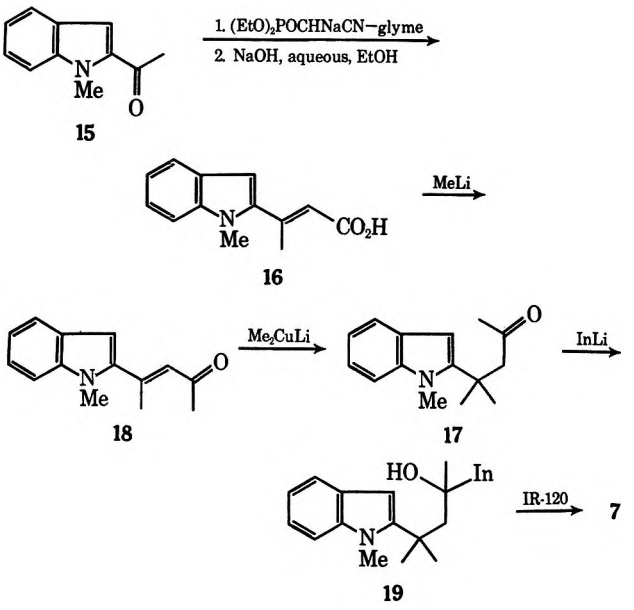
(14) G. Büchi, R. E. Manning, and S. A. Monti, *J. Amer. Chem. Soc.*, **86**, 4631 (1964).

(15) H. M. Kissman, D. W. Farnsworth, and B. Witkop, *ibid.*, **74**, 3948 (1952).

(16) K. T. Potts and P. R. Liljegren, *J. Org. Chem.*, **28**, 3202 (1963).

phenyldimethylcarbinol.[17] Independent evidence for structure **7** was obtained by the synthetic route outlined in Scheme IV.

SCHEME IV

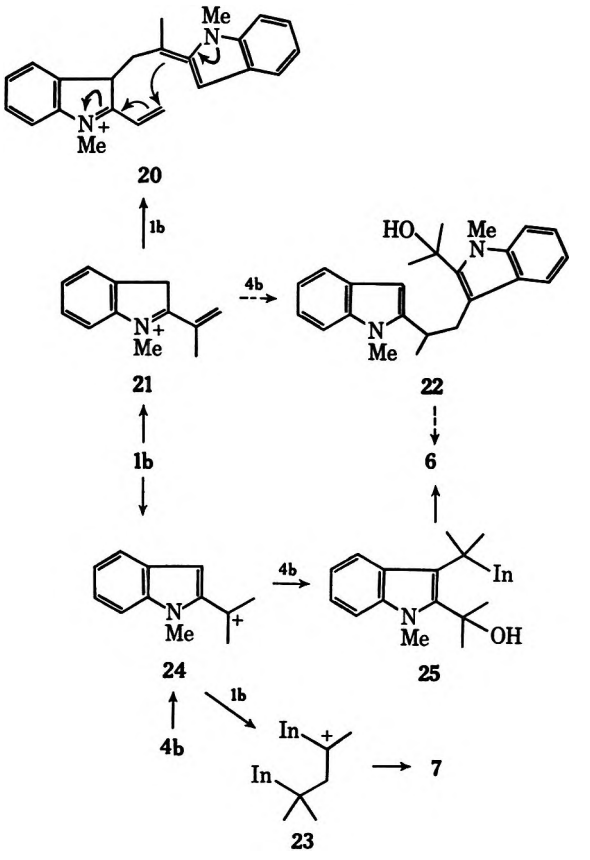


When either the vinylindole **1b** or tertiary alcohol **4b** was refluxed in 95% ethanol containing Amberlite IR-120 resin, a nearly identical mixture of two compounds was obtained with a new dimer **6** predominating over dimer **7**. The structure of the new dimer was based upon its nuclear magnetic spectrum which revealed a three-proton doublet at δ 1.13 (J = 7 Hz), a six-proton singlet, δ 2.16, and a one-proton multiplet centered at δ 3.45 in addition to other signals. Irradiation at δ 3.45 caused the high-field multiplet to collapse to a singlet. This data along with the lack of any indole C_3-H signal argued for structure **6** to be assigned to the second dimer. Finally, subjection of alcohol **4b** to Florisil conditions produced the same two dimeric species as did the IR-120 resin; however, the product distributions were essentially reversed.

The thermal reactivity of both vinylindoles is reflected in their ability to undergo Diels–Alder reactions with *N*-phenylmaleimide.[18] Whereas 1-methyl-2-vinyl indole formed adduct **14a** in 1 day at room temperature, upward to 1 week was required to prepare adduct **14b** from vinylindole **2b**.

Some general mechanistic considerations can be gleaned from these data (Scheme V). The striking fact is that dimer **8** is formed from olefin **1b** under Florisil catalysis without the formation of dimer **6** which is derived under the same conditions from alcohol **4b**. This observation points out the essential dehydrating nature of the Florisil medium and the hydrating conditions used with IR-120 resin. Although both systems are capable of producing cations **21** and **24**, the Florisil–benzene favors vinylindole **1b** as the second reactive species, whereas IR-120–alcohol favors alcohol **4b** (or its ethyl ether). In addition, the similarity of product distribution in treating either the olefin or alcohol

SCHEME V



with IR-120 resin indicates that the same reactive intermediates are formed in both experiments. The reversal of yields in treating alcohol **4b** with Florisil–benzene reflects the higher concentration of **1b** relative to the IR-120–ethanol conditions. Although dimer **6** can be formally derived by two different pathways while dimer **8** can only be formed by one route, it is likely that dimer **6** is formed *via* intermediate **25** since **22** has the same substitution pattern as intermediate **20** and could lead to dimer **8**.

Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories and Bernhardt Microanalytische Laboratorium. Infrared spectra were determined on a Perkin-Elmer Model 421 or 237B spectrometer. Nuclear magnetic resonance spectra were obtained with Varian Model A-60, A-60A, or HA-100 spectrometers. Chemical shifts are reported in δ units using tetramethylsilane as internal reference. Ultraviolet spectra were recorded on a Bausch and Lomb Spectronic 505 or a Cary 11S recording spectrometer. Absorptions are reported as λ_{max} (ϵ) in nanometer units. Mass spectra were obtained on an AEI MS-9 spectrometer or a Hitachi RMU-6.

Except where noted, solvents were reagent grade and were used as received. Analytical thin layer plates were run using 3:1 benzene–hexane as the moving phase unless otherwise noted. In all work-up procedures the drying process involved treatment with anhydrous magnesium sulfate and filtering prior to evaporation.

1-Methyl-2-vinylindole (1a).—In a three-necked flask fitted with a serum cap, addition funnel, and reflux condenser was placed 14.68 g (0.0512 mol) of methyltriphenylphosphonium bromide and 250 ml of dry ether. To this stirred suspension, under nitrogen, 22.0 ml (0.0343 mol) of 1.56 *M* *n*-butyllithium in hexane was added by a syringe and the mixture was refluxed for 2 hr. A solution of 4.00 g (0.0252 mol) of 1-methyl-2-formyl-

(17) A. Dierichs and E. Preu, *Chem. Ber.*, **90**, 1208 (1957); N. G. Polyanski, S. M. Markevich, N. L. Potudina, and A. N. Burova, *Neftekhimiya*, **2**, 348 (1962); *Chem. Abstr.*, **58**, 8938 (1963).

(18) D. Beck and K. Schenker, *Helv. Chem. Acta*, **51**, 260, 264 (1968).

indole[19] in 100 ml of dry ether was then added at room temperature and refluxing was continued for 2 hr. After being cooled in an ice bath, saturated sodium sulfate solution was added and the ether layer was separated, washed four to five times with cold water, dried, and evaporated at room temperature. The residue was thoroughly washed with petroleum ether (bp 30–60°) and the combined washes were evaporated. The petroleum ether wash was repeated and evaporation gave 2.54 g (64%) of a clear yellow liquid whose spectral properties were in accord with the desired product: nmr ($CDCl_3$) δ 3.50 (3 H, s), 5.24 (1 H, dd, J = 11 and 2 Hz), 5.69 (1 H, dd, J = 17.5 and 2 Hz), 6.62 (1 H, s), 6.68 (1 H, dd, J = 17.5 and 11 Hz), and 6.90–7.80 (4 H, m); uv λ_{max} (EtOH) 228 nm (ϵ 25,700) and 305 (13,700).

Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.04; H, 6.99; N, 8.81.

Thermal Dimerization of 1-Methyl-2-vinylindole. 9-Methyl-1,2,3,4-tetrahydro-4-[2′-(1′-methylindolyl)]carbazole (2).—A solution of 0.50 g (3.18 mmol) of vinylindole **1a** in 8 ml of toluene was refluxed under nitrogen for 30 hr. Evaporation of the solvent gave an orange oil which afforded 0.364 g (73%) of a tan solid from benzene–methanol. Chromatography on a short Florisil column with benzene and trituration of the residual pale green oil (0.349 g) with ether gave a light tan solid, mp 140–145°. Two recrystallizations from ether failed to improve the purity, but recrystallization from benzene–methanol gave a white solid material: mp 142–144°; nmr ($CDCl_3$) δ 1.56–2.92 (6 H, m), 3.53 (3 H, s), 3.62 (3 H, s), 4.28–4.60 (1 H, m), 6.10 (1 H, s), and 6.68–7.60 (8 H, m); uv λ_{max} (MeOH) 225 nm (ϵ 66,500), 286 (14,400); mass spectrum (70 eV) m/e (rel intensity) 314 (34), 158 (21.5), 157 (100), 156 (16), and 78.5 (metastable).

Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.77; H, 7.40; N, 8.88.

Reaction of 1-Methyl-2-vinylindole with Florisil. 9-Methyl-1,2,3,4-tetrahydro-3-[2′-(1′-methylindolyl)]carbazole (3).—A slurry of 0.351 g (2.17 mmol) of vinylindole **1a** and 20 g of Florisil in 40 ml of benzene was stirred at room temperature overnight. The mixture was filtered and, after thoroughly washing the dark red-brown Florisil with hot benzene, the combined benzene solutions were evaporated to give 0.294 g of a yellow oil which showed two spots on an analytical thin layer plate. The nmr spectrum indicated that the mixture consisted of dimer **2** (smaller R_f) and an isomeric dimer in a 1:3 ratio. Chromatography on Florisil with 1:1 benzene–petroleum ether gave 0.196 g (56%) of a white solid, mp 130–144°. Recrystallization from benzene–methanol afforded 0.108 g of white prisms: mp 153–153.5°; nmr ($CDCl_3$) δ 2.09–3.58 (7 H, m), 3.62 (3 H, s), 3.74 (3 H, s), 6.38 (1 H, s), and 6.90–7.80 (8 H, m); uv λ_{max} (MeOH) 227 nm (ϵ 68,000), 283 (17,500), and 290 (15,900); mass spectrum (70 eV) m/e (rel intensity) 315 (29), 314 (100), 286 (46), 285 (52), 271 (29), 270 (25), 260.5 (metastable), 183 (46), and 157 (27).

Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.78; H, 7.01; N, 9.33.

1-Methyl-2-(α-hydroxyethyl)indole (4a).—A mixture of 1.0 g (5.8 mmol) of 1-methyl-2-acetylindole[20] and 0.50 g (13.2 mmol) of sodium borohydride in 40 ml of ethanol containing 2 ml of 10% aqueous sodium hydroxide was stirred at 0° for 2 hr. Addition of water, ether extraction, and evaporation of the dried ether solution led to a pale green oil which upon standing with a small amount of benzene in a freezer overnight gave 0.93 g of solid material. Recrystallization from ether–petroleum ether gave 0.86 g (86%) of white needles: mp 56.5–57.5°; nmr ($CDCl_3$) δ 1.55 (3 H, d, J = Hz), 1.97 (1 H, s), 3.60 (3 H, s), 5.81 (1 H, q, J = 7 Hz), 6.35 (1 H, s), and 6.85–7.70 (4 H, m); ir ($CHCl_3$) 3650 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.08; H, 7.44; N, 7.92.

Reaction of Alcohol 4a with Amberlite IR-120 Ion Exchange Resin. 5,6,11,12-Tetramethyl-6,12-dihydroindole[3,2-*b*]carbazole (5).—A mixture of 0.50 g (2.86 mmol) of alcohol **4a** and 0.525 g of Amberlite IR-120 ion exchange resin in 6 ml of 95% ethanol was refluxed overnight under nitrogen. Benzene was added and the dried solution was evaporated to yield 0.465 g of a tacky, pale green gum. Chromatography on Florisil with 1:1 benzene–petroleum ether followed by recrystallization of the residue from benzene–methanol gave 0.267 g (55%) of pale green solid. Several recrystallizations from benzene–methanol led to a semipure material (mp 235–255°), but sublimation [180–200° (1 μ)] gave a pale yellow solid: mp 262–264°; nmr ($CDCl_3$) δ 1.63 (3 H, d, J = 7 Hz), 3.79 (3 H, s), 4.47 (1 H, q, J = 7 Hz), and 6.91–7.80 (4 H, m); uv λ_{max} (MeOH) 233 nm (ϵ 77,000), 286 (13,600), and 294 (13,300); mass spectrum (70 eV) m/e (rel intensity) 314 (41), 299 (80), 285 (24), 284 (100), 269 (23), 254 (7), 157 (7), and 142 (33).

Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N; 8.91. Found: C, 84.25; H, 6.89; N, 9.00.

1-Methyl-2-isopropenylindole (1b).—The procedure was the same as was used for the preparation of 1-methyl-2-vinylindole (**1a**). From 4.32 g (0.025 mol) of 1-methyl-2-acetylindole the work-up gave 5.03 g of an orange oil. Chromatography on a short Florisil column with petroleum ether afforded 3.35 g (78%) of a colorless liquid: bp 95° (0.07 mm); nmr ($CDCl_3$) δ 2.13 (3 H, s), 5.06 (1 H, s), 5.22 (1 H, s), 6.35 (1, H, s), and 6.85–7.60 (4 H, m); uv λ_{max} (EtOH) 226 nm (ϵ 25,200) and 295 (15,800).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.67; H, 8.00; N, 8.23.

1-Methyl-2-(α-hydroxylisopropyl)indole (4b).—To a solution of 4.0 g (0.021 mol) of 1-methyl-2-acetylindole in 100 ml of dry ether was added 50 ml (0.024 mol) of 0.48 *M* methylmagnesium bromide in ether. After the addition was completed, the mixture was stirred for 10 min at room temperature and then decomposed with saturated sodium sulfate solution. The ether was decanted and, after thoroughly washing the residual salts with ether, the combined ether solutions were dried and evaporated. Trituration of the resulting oil with ether–petroleum ether gave 3.1 g (78%) of a white solid. Recrystallization from petroleum ether provided silky white crystals: mp 90–91°; nmr ($CDCl_3$) δ 1.52 (6 H, s), 3.71 (3 H, s), 6.09 (1 H, s), and 6.80–7.80 (4 H, m).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.36; H, 8.12; N, 7.51.

Reaction of Alcohol 4b with Amberlite IR-120. 5,6,6,11,12-Pentamethyl-5,11,12,13-tetrahydro-6*H*-indolo[3,2-*c*]cyclohept[*b*]-indole (6).—A mixture of 0.20 g (1.06 mmol) of alcohol **4b** and 0.225 g of Amberlite IR-120 ion exchange resin in 5 ml of 95% ethanol were refluxed overnight under nitrogen. Benzene was added and evaporation of the dried solution gave 0.156 g of a yellow oil whose thin layer chromatogram showed three spots of almost identical R_f. The nmr spectrum of the crude material indicated a 1:2:7 mixture of vinylindole **1b**, dimer **7**, and dimer **6**, respectively; crystallization from benzene–methanol afforded 0.046 g (25%) of a tan solid, mp 236–241°. Chromatography on a short Florisil column with benzene and trituration of the residue with petroleum ether gave 0.028 g of white solid. Recrystallization from benzene–methanol gave colorless prisms: mp 247–248°; nmr ($CDCl_3$) δ 1.13 (3 H, d, J = 7 Hz), 2.16 (6 H, s), 3.23 (2 H, m), 3.33–3.56 (1 H, m), 3.67 (3 H, s), 3.94 (3 H, s), and 6.90–8.00 (8 H, m); uv λ_{max} (EtOH) 232 nm (ϵ 72,000), 287 (15,300), and 294 (14,300); mass spectrum (70 eV) m/e (rel intensity) 342 (39), 328 (48), 327 (100), 312 (7), 297 (24), 282 (8), 163 (24), and 156 (37).

Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.15; N, 8.18. Found: C, 84.09; H, 7.91; N, 8.19.

Reaction of Alcohol 4b with Florisil. 1,3,3,4-Tetramethyl-1-[2′-(1′-methylindolyl)]-1,2,3,4-tetrahydrocyclopent[*b*]indole (7).—A slurry of 0.200 g (1.06 mmol) of alcohol **4b** and 12 g of Florisil in 25 ml of benzene was stirred at room temperature overnight. The benzene was decanted and, after thoroughly extracting the blue-black Florisil with hot chloroform, the combined organic solutions were evaporated to give an oil whose nmr spectrum indicated a 2:1 mixture of dimers **7** and **6**, respectively. Chromatography on a short Florisil column with benzene and low temperature crystallization of the residue from ether–petroleum ether afforded 0.079 g (43%) of a solid material, mp 137–147°. Sublimation [145–150° (1 μ)] and two recrystallizations from ethanol gave 0.031 g of white needles: mp 160–162°; nmr ($CDCl_3$) δ 1.38 (3 H, s), 1.49 (3 H, s), 1.88 (3 H, s), 2.90 (1 H, d, J = 13 Hz), 2.55 (1 H, d, J = 13 Hz), 3.57 (3 H, s), 3.65 (3 H, s), 6.23 (1 H, s), and 6.70–7.50 (8 H, m); uv λ_{max} (EtOH) 299 nm (ϵ 64,000), 279.5 (16,400), 285 (18,200), and 293 (16,400); mass spectrum (70 eV) m/e (rel intensity) 342 (66), 328 (64), 327 (100), 312 (9), 297 (12), 282 (5.5), 196 (32), and 156 (40).

Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.82; H, 8.02; N, 8.22.

Reaction of 1-Methyl-2-isopropenylindole (1b) with Florisil. 1,3,9-Trimethyl-1,2,3,4-tetrahydro-3-[2′-(1′-methylindolyl)]-carbazole (8).—A slurry of 1.00 g (5.51 mmol) of vinylindole **1b**

(19) K. Hoffman, A. Rossi, and J. Kebrle, German Patent 1,093,365 (1958); *Chem. Abstr.*, **56**, 4735*f* (1962).

(20) O. Diels and A. Kollisch, *Chem. Ber.*, **44**, 266 (1911).

and 50 g of Florisil in 100 ml of benzene was stirred at room temperature for 5 days. The mixture was filtered and, after thorough washing of the dark brown Florisil with hot chloroform, the combined solutions were evaporated to give 0.927 g of a brown oil which showed two spots on an analytical thin layer plate. The nmr spectrum of the crude residue indicated a 1:1 mixture of dimers 8 (smaller R_f) and 7. Trituration of the residue with benzene–methanol gave 0.189 g of a white solid, mp 204–207°.

The filtrate was concentrated and chromatographed on a short Florisil column. Elution with hexane removed the nonindolic material; elution with 1:3 benzene–hexane (fraction 2) afforded 0.381 g of a viscous oil. Trituration with ethanol gave 0.173 g of a pale yellow solid (mp 120–160°) which partially dissolved in benzene leaving 0.014 g of a white solid, mp 196–200°. Elution with 1:1 benzene–hexane (fraction 3) then gave 0.159 g of an orange liquid from which 0.013 g of solid, mp 203–205°, was obtained by trituration with ethanol. The solids were combined (0.216 g, 22%) and recrystallized from a minimal amount of benzene to give 0.163 g of chunky white crystals, mp 207–209°. Another recrystallization afforded analytically pure material: mp 207.5–208.5°; nmr ($CDCl_3$) δ 1.34 (3 H, d, J = 6 Hz), 1.56 (3 H, s), 1.78 (1 H, dd, J = 12 and 16 Hz), 2.50–3.00 (3 H, m), 3.45 (3 H, s), 3.54 (1 H, d, J = 14 Hz), 3.82 (3 H, s), 6.02 (1 H, s), and 6.70–7.70 (8 H, m); uv λ_{max} (EtOH) 232 nm (ϵ 55,000), 286 (14,200), and 292 (14,200); mass spectrum (70 eV) m/e (rel intensity) 342 (15), 327 (1), 171 (100), and 85.5 (metastable).

Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.09; H, 7.70; N, 8.08.

The mother liquors from fractions 2 and 3 were concentrated and crystallized from ethanol to give a total of 0.144 g of white solid, mp 145–60°. This material was sublimed [145–150° (1 μ)] and twice recrystallized from ethanol to give 0.010 g of clear needle-like crystals, mp 160.5–162°, identical in all respects with dimer 7.

3,3,4-Trimethyl-1,2,3,4-tetrahydrocyclopent[*b*]indol-1-one (12a).—In a 50-ml flask was placed 1.06 g (6.71 mmol) of methyl 3,3-dimethyllevulinate (prepared from the acid[21] by reaction with excess diazomethane) and 0.99 g (7.39 mmol) of α-methylphenylhydrazine. To this mixture was added, with stirring, 4.0 g of polyphosphoric acid and, after the initial exothermic reaction had subsided (the temperature rising to 75–80°), the mixture was heated at 125–130° for 2 hr. After cooling to room temperature, the residual hard mass was carefully dissolved in water with cooling and the solution was thoroughly extracted with methylene chloride. The extracts were washed with dilute base and water, dried, and evaporated to give 0.79 g of a dark brown solid. Chromatography on Florisil with 9:1 benzene–ether and crystallization of the residue from benzene–hexane afforded 0.38 g (27%) of light gray flakes, mp 150–153°. Recrystallization from benzene–hexane gave white flakes: mp 154.4–155.5°; nmr ($CDCl_3$) δ 1.58 (6 H, s), 2.88 (2 H, s), 3.83 (3 H, s), 7.15–8.10 (4 H, m); ir ($CHCl_3$) 1680 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.04; H, 6.81; N, 6.34.

3,3,4-Trimethyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (12b).—In a three-necked flask fitted with addition funnel and reflux condenser was placed 0.18 g (4.70 mmol) of lithium aluminum hydride, 0.47 g (3.52 mmol) of aluminum chloride, and 5 ml of dry tetrahydrofuran. To this stirred suspension, under nitrogen, a solution of 0.100 g (4.70 mmol) of ketone 12a and 0.14 g (1.04 mmol) of aluminum chloride in 15 ml of dry tetrahydrofuran was added dropwise and the mixture refluxed overnight. After cooling to 0°, the mixture was carefully decomposed with saturated sodium sulfate solution and extracted with benzene. The extracts were washed with water, dried, and evaporated to give a clear oil which solidified on standing. Chromatography on a short Florisil column with benzene followed by sublimation [50° (0.5 μ)] of the residue gave 0.035 g (37%) of clear flakes: mp 74–75°; nmr ($CDCl_3$) δ 1.38 (6 H, s), 2.13–2.95 (4 H, m, A_2B_2), 3.67 (3 H, s), 6.90–7.60 (4 H, m); mass spectrum (70 eV) m/e (rel intensity) 199 (62), 185 (34), 184 (100), 169 (21), and 168 (28).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.43; H, 8.68; N, 6.98.

1,1-Dideuterio-3,3,4-trimethyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (12c).—Ketone 12a (0.200 g, 0.94 mmol) was reduced with lithium aluminum deuteride as described above. The residue from benzene extraction (0.18 g) was purified by low temperature crystallization from methanol and the product (0.101 g, 54%) was obtained as clear flakes: mp 74.5–75.5°; nmr ($CDCl_3$) δ 1.39 (6 H, s), 2.31 (2 H, s), 3.69 (3 H, s), 6.90–7.60 (4 H, m); mass spectrum (70 eV) m/e (rel intensity) 201 (31), 186 (100), 171 (8), and 170 (11).

Reaction of 1-Methyl-2-vinylindole with *N*-Phenylmaleimide. 6-Methyl-2-phenyl-1,3-dioxo-2,3,3a,4,5,10c-hexahydro[1*H*]pyrrolo[3,4-*c*]carbazole (14a).—A mixture of 0.25 g (1.59 mmol) of vinylindole 1a and 0.25 g (1.45 mmol) of *N*-phenylmaleimide in 5 ml of benzene was stirred under nitrogen at room temperature for 30 hr. After 16 hr the clear yellow solution had become milky white with precipitated solid. The precipitate was filtered, washed with benzene, and air-dried to give 0.292 g (61%) of a white solid, mp 188–188.5°. Recrystallization from benzene–hexane gave analytically pure material: mp 189–190°; nmr ($CDCl_3$) δ 1.33–1.92 (4 H, m), 3.26–3.54 (1 H, m), 3.58 (3 H, s), 4.41 (1 H, d, J = 7.5 Hz), and 7.00–8.17 (9 H, m); ir ($CHCl_3$) 1710 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 331 (49), 330 (100), 210 (23), 184 (26), 183 (100), 182 (100), 181 (33), 168 (20), and 167 (64).

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.58; H, 5.80; N, 8.14.

Reaction of 1-Methyl-2-isopropenylindole with *N*-Phenylmaleimide. 5,6-Dimethyl-2-phenyl-1,3-dioxo-2,3,3a,4,5,10c-hexahydro[1*H*]pyrrolo[3,4-*c*]carbazole (14b).—A mixture of 0.25 g (1.46 mmol) of vinylindole 1b and 0.25 g (1.45 mmol) of *N*-phenylmaleimide in 10 ml of benzene was stirred, under nitrogen, at room temperature for 7 days. Hexane was added and 0.32 g of a yellow-orange solid was collected. Recrystallization from benzene–hexane afforded 0.047 g (9%) of white prisms: mp 209–213.5° (another recrystallization raised the melting point to 210.5–212°); nmr ($CDCl_3$) δ 1.23 (3 H, d, J = 9 Hz), 1.80–3.60 (3 H, m), 3.61 (3 H, s), 4.44 (1 H, d, J = 9 Hz), and 6.80–8.20 (9 H, m); ir ($CDCl_3$) 1710 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 344 (6), 343 (26), 342 (100), 208 (17), 197 (16), 182 (53), and 167 (26).

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.65; H, 6.10; N, 7.90.

3-[2′-(1′-Methylindolyl)]but-2-enoic Acid (16).—In a 1-l. three-necked flask fitted with a thermometer, addition funnel, and reflux condenser was placed 2.64 g (0.055 mol) of 50% sodium hydride suspension and 100 ml of dry 1,2-dimethoxyethane (glyme). To this stirred suspension, under nitrogen, a solution of 10.7 g (0.06 mol) of diethyl cyanomethylphosphonate in 50 ml of dry glyme was added so as to keep the temperature below 10° with the aid of external cooling. After being stirred at room temperature until hydrogen evolution ceased (approximately 1.5 hr), the mixture was cooled below 10° while a solution of 8.65 g (0.05 mol) of 1-methyl-2-acetylindole in 100 ml of dry glyme was added. The mixture was stirred at room temperature for 2 hr, decomposed with saturated sodium sulfate solution, and extracted with ether. The combined extracts were then washed with water, dried, and evaporated.

The residue was dissolved in 100 ml of ethanol, 25% aqueous sodium hydroxide solution was added until two layers remained, and the mixture was refluxed, under nitrogen, overnight. Following separation of the layers, the organic layer was washed with 10% sodium hydroxide solution and the combined aqueous solutions were washed twice with ether and then acidified with cold concentrated hydrochloric acid. The acid solution was extracted with ether and the combined extracts were dried and evaporated to give 8.0 g of an orange solid (after drying in a vacuum desiccator). Recrystallization from ether–petroleum ether followed by sublimation [110–125° (0.02 mm)] afforded 5.25 g (50%) of yellow needles, mp 146–149°. Sublimation of the material which was recrystallized several times from ether–petroleum ether gave pale yellow needles: mp 150.5–151.5°; nmr ($CDCl_3$) δ 2.61 (3 H, s), 3.74 (3 H, s), 5.98 (1 H, s), 6.62 (1 H, s), 6.90–7.70 (4 H, m), and 11.03 (1 H, s); ir ($CHCl_3$) 3500–2500 (broad OH), 1695, and 1610 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.78; H, 5.82; N, 6.16.

Evaporation of the ether solution containing the neutral material from the hydrolysis gave an oil which crystallized on trituration with ether. This material, the amide of the acid, was twice recrystallized from methylene chloride–ether to give 0.200 g of a fluffy white solid: mp 137–138°; nmr ($CDCl_3$) δ 2.53 (3 H, d, J = 1.5 Hz), 3.68 (3 H, s), 5.76 (2 H, broad s), 5.93 (1 H, d, J = 1.5 Hz), 6.55 (1 H, s), and 6.90–7.80 (4 H, m).

(21) N. R. Easton and R. D. Dillard, *J. Org. Chem.*, **27**, 3602 (1962).

When the reaction was run using 0.865 g (5.0 mmol) of 1-methyl-2-acetylindole and the crude residue washed several times with petroleum ether to remove the mineral oil, 0.959 g (98%) of the nitrile was obtained as a light orange oil: nmr ($CDCl_3$) δ 2.46 (3 H, s), 3.67 (3 H, s), 5.36 (1 H, s), 6.68 (1 H, s), and 6.90–7.80 (4 H, m); ir ($CHCl_3$) 2220 (conjugated CN) and 1655 cm^{-1}.

4-[2′-(1′-Methylindolyl)]pent-3-en-2-one (18).—In a 250-ml three-necked flask fitted with a serum cap, an addition funnel, and a reflux condenser was placed 5.0 g (0.023 mol) of butenoic acid **16** and 125 ml of dry ether. To this stirred solution, under nitrogen, 26.0 ml (0.061 mol) of 2.35 *M* methyllithium in ether was added by a syringe so as to maintain a gentle reflux. The mixture was stirred at room temperature for 45 min and then poured into a cold, saturated solution of ammonium chloride. After separating the ether layer, the aqueous layer was washed with ether and the combined organic solutions were washed with 10% aqueous sodium hydroxide and water, dried, and evaporated to give 4.61 g (93%) of an orange oil which showed essentially one spot on an analytical thin layer plate (4:1 benzene–ethyl acetate). The material was passed through a short Florisil column with benzene prior to use: nmr ($CDCl_3$) δ 2.11 (3 H, s), 2.43 (3 H, s), 3.52 (3 H, s), 6.14 (1 H, s), 6.42 (1 H, s), and 6.70–7.50 (4 H, m); ir ($CHCl_3$) 1675 (conjugated C=O), and 1590 cm^{-1}.

4-Methyl-4-[2′-(1-methylindolyl)]pentan-2-one (17).—A solution of lithium dimethylcopper(I) was prepared under nitrogen by adding 19.2 ml (0.045 mol) of 2.35 *M* methyllithium in ether *via* a syringe to a suspension of 4.28 g (0.0224 mol) of copper(I) iodide in 75 ml of dry ether at 0°. To the cold stirred suspension a solution of 2.39 g (0.011 mol) of pentenone **18** in 80 ml of dry ether was added and the mixture was stirred at 0° for an additional 30 min. The mixture was poured into an aqueous ammonium chloride solution and, after the ether layer separated, the aqueous layer was extracted with ether and the combined organic solutions were washed with water, dried, and evaporated to give 2.28 g (89%) of an orange liquid. The crude product showed essentially one spot (R_f considerably larger than that of the starting material) on an analytical thin layer plate (4:1 benzene–ethyl acetate). The nmr spectrum indicated that the only contaminants were those present in the starting material, *i.e.*, no 1,2 addition had occurred. The liquid was chromatographed on Florisil first with petroleum ether to remove impurities and then with benzene. Evaporation of the benzene solvent led to a pale yellow liquid whose spectra were in accord with the desired product: nmr ($CDCl_3$) δ 1.51 (6 H, s), 1.78 (3 H, s), 2.80 (2 H, s), 3.81 (3 H, s), 6.30 (1 H, s), and 6.90–7.70 (4 H, m); ir ($CHCl_3$) 1700 cm^{-1}.

Preparation of the oxime in the usual fashion gave white prisms from ethanol, mp 161–163°.

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.77; H, 7.85; N, 11.53.

4-Methyl-2,4-di[2′-(1′-methylindolyl)]pentan-2-ol (19).—In a three-necked flask fitted with a serum cap, an addition funnel, and a reflux condenser was placed 2.06 g (0.016 mol) of 1-methylindole[22] in 40 ml of dry ether. To the stirred solution, under nitrogen, 10.0 ml (0.0156 mol) of 1.56 *M* *n*-butyllithium in hexane was added *via* a syringe and the mixture was then refluxed for 6 hr. After cooling to room temperature, a solution of 1.20 g (0.0052 mol) of ketone **17** in 20 ml of ether was added and the mixture was then refluxed for 3 hr. The solution was cooled and, after decomposing with saturated sodium sulfate solution, the ether layer was separated, the aqueous layer was extracted with ether, and the combined ether solutions were washed with water, dried, and evaporated. The residue was chromatographed on Florisil, first with petroleum ether to remove excess 1-methylindole and then with benzene. Evaporation of solvent gave 1.46 g (77%) of an orange glass which showed one major spot on an analytical thin layer plate. The crude alcohol could not be crystallized, sublimed, or chromatographed without extensive decomposition and was used in the subsequent reaction without further purification: nmr ($CDCl_3$) δ 1.27 (3 H, s), 1.34 (3 H, s), 1.43 (3 H, s), 2.52 (2 H, s), 2.72 (1 H, s), 3.84 (3 H, s), 3.90 (3 H, s), 6.23 (1 H, s), 6.28 (1 H, s), and 6.80–7.70 (8 H, m).

1,3,3,4-Tetramethyl-1-[2′-(1′-methylindolyl)]-1,2,3,4-tetrahydrocyclopent[*b*]indole (7) from Alcohol 19.—A mixture of 0.273 g (0.769 mmol) of alcohol **19** and 0.30 g of Amberlite IR-120 ion exchange resin in 10 ml of 95% ethanol was refluxed, under nitrogen, overnight. After cooling benzene was added and the mixture was dried and evaporated to give 0.246 g of a dark brown oil. Chromatography on Florisil with benzene afforded 0.201 g of an oil which on standing with ether–petroleum ether gave 0.042 g (16%) of a white solid, mp 159–161°, identical with dimer **7** on the basis of their mixture melting point and identical nmr spectra.

Registry No.—**1a**, 29124-06-9; **1b**, 29124-07-0; **2**, 29124-08-1; **3**, 29124-09-2; **4a**, 29124-10-5; **4b**, 29124-11-6; **5**, 29124-12-7; **6**, 29124-13-8; **7**, 29199-39-1; **8**, 29124-14-9; **12a**, 29124-15-0; **12b**, 29124-16-1; **12c**, 29124-17-2; **14a**, 29124-18-3; **14b**, 29124-19-4; **16**, 29124-20-7; **16** amide, 29124-21-8; **16** nitrile, 29124-22-9; **17**, 29199-40-4; **17** oxime, 29124-23-0; **18**, 29124-24-1; **19**, 29124-25-2.

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(22) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954); W. E. Noland, W. C. Kuryla, and R. F. Lange, *J. Amer. Chem. Soc.*, **81**, 6010 (1959).

Photooxidation of Hexamethylbenzene and Related Aromatic Systems

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Hexamethylbenzene, when subjected to the conditions of dye-sensitized photooxidation in methanol–benzene, forms pentamethylbenzyl methyl ether (**2**), tetramethylphthalyl bismethyl ether (**3**), and tetramethylphthalide (**4**) in high yields. The diether **3** was shown to be a product of a second-stage photooxidation of the monoether **2**. Pentamethylbenzaldehyde yields tetramethylphthalide (**4**) under the above conditions. A mechanism for these transformations is discussed.

In earlier studies,[1] we have investigated the dye-sensitized photooxidation of aromatic compounds in the cyclophane series where steric constraints result in nonplanarity of the ring systems. In the above cases, reactions of the strained aromatic systems with singlet oxygen yielded transannular peroxides which then underwent solvolysis followed by intramolecular Diels–Alder reactions.

In other studies on the photooxidation of aromatic hydrocarbons, benzylic C–H groups have been oxidized,[2] phenolic systems have been hydroxylated,[3] and, in some instances, cleavage of the aromatic ring has taken place.[3] In general, the involvement of singlet oxygen in these oxidation processes has not been clearly demonstrated. In fact, the bulk of the observations may be explained in terms of a radical pathway in which the only role played by oxygen is that of a radical scavenger.[3,4] The present work describes our investigations on the dye-sensitized photooxidation of aromatic hydrocarbons containing benzylic carbon–hydrogen bonds in crowded environments.

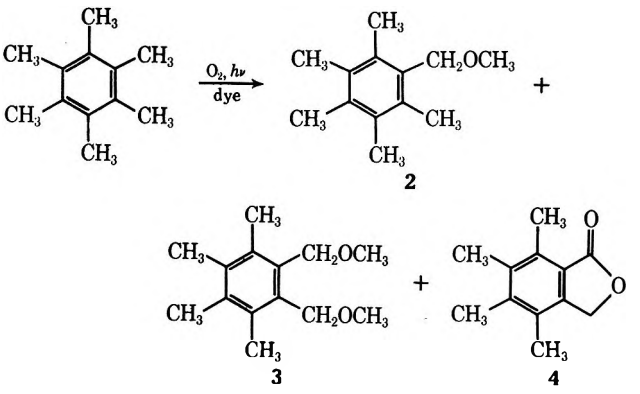
Hexamethylbenzene, subjected to the conditions of methylene blue sensitized photooxidation in methanol–benzene (1:1) at room temperature, was converted in good yield to a mixture of three products, identified[5] on the basis of spectroscopic data as pentamethylbenzyl methyl ether (**2**, 36%), tetramethylphthalyl bismethyl ether (**3**, 42%), and tetramethylphthalide (**4**, 9%) (Scheme I).[6]

The structures **2**–**4** were confirmed by the following sequences. The bismethyl ether **3** was converted to the dichloride **5** which, on solvolysis, yielded the diol **6**. Compound **6** was identical (physical and spectroscopic properties) with the material obtained from the $LiAlH_4$ reduction of the phthalide **4** (Scheme II).

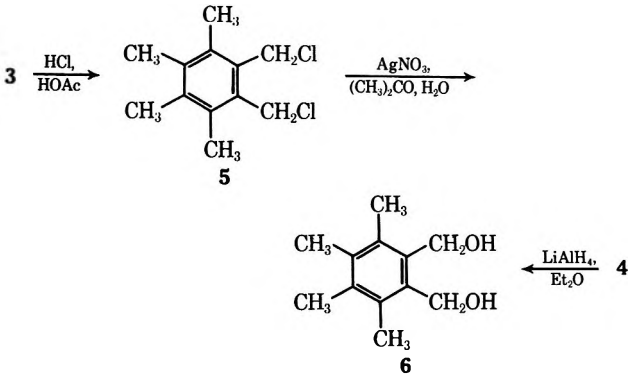
The monomethyl ether **2** was similarly converted to the monochloride **7** which underwent solvolysis to the benzyl alcohol **8**. Oxidation of the latter with MnO_2 yielded the benzaldehyde **9** (Scheme III).

Formation of products **2**–**4** in high yield by the above oxygenation is of interest not only in connection with the potential use of this reaction in synthesis but also in relation to possible analogies of these transformations with oxidations of aromatic nuclei in naturally occurring systems.[7] The following studies relate

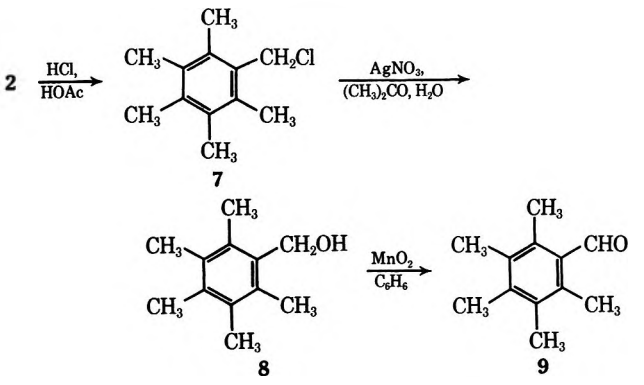
SCHEME I



SCHEME II



SCHEME III



(1) H. H. Wasserman and P. M. Keehn, *J. Amer. Chem. Soc.*, **88**, 4522 (1966); unpublished results on the photooxidation of *syn*-1,4-[2,2]-naphthalenophane.

(2) K. S. Wei and A. H. Adelman, *Tetrahedron Lett.*, 3297 (1969).

(3) T. Matsuura, N. Yoshimura, A. Nishinaya, and I. Saito, *ibid.*, 1669 (1969); T. Matsuura, A. Nishinaya, N. Yoshimura, and T. Arai, *ibid.*, 1673 (1969); I. Saito, S. Kato, and T. Matsuura, *ibid.*, 239 (1970).

(4) For a discussion of this type of process and pertinent references, see C. S. Foote, *Science*, **162**, 963 (1968).

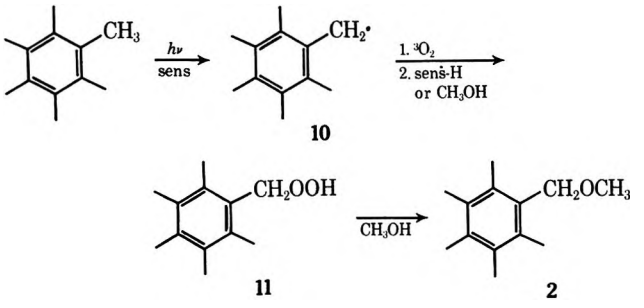
(5) Products were, in general, characterized by their nmr spectra and physical properties. Thus, for example, the bismethyl ether **3** shows a typical symmetrical pattern in the nmr for the four aryl methyl groups at τ 7.69 and 7.78 corresponding to the *o*- and *m*-methyls, respectively. The same pattern of absorption is shown for the methyl groups in the *o*-dichloride **5** (τ 7.62 and 7.75) and the diol **6** (τ 7.64 and 7.77).

(6) The yields given are based on unrecovered starting material.

(7) See, for example, J. W. Foster in "Oxygenases," Academic Press, New York, N. Y., 1962.

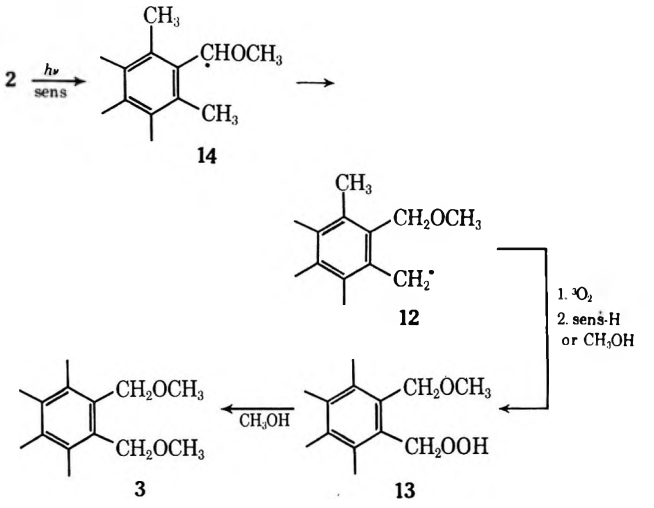
to the mechanism of this process. On varying the duration of photooxidation, we found that the yield of monomethyl ether **2**, higher at shorter times, varied inversely with that of the bismethyl ether **3**. Thus, 14-day oxidations yielded 36% **2** and 42% **3**, while 8-day reactions gave 82% **2** and 12% **3**. We have accordingly concluded that the bisether **3** arises *via* a second-stage photooxidation of the monoether **2**. This view was confirmed by the isolation of ether **2**, exclusively, in low conversion runs (20%, after 7 days). Furthermore, when pentamethylbenzyl methyl ether (**2**) was subjected to the condition of photooxidation, it was completely transformed to the tetramethylphthalyl bismethyl ether (**3**).[8]

In the sequence below we suggest a mechanism for the production of the ether **2**.[9] Initial hydrogen abstraction with formation of the benzyl radical **10** is followed by uptake of triplet oxygen leading to the hydroperoxide **11**. Methanol solvolysis of the hydroperoxide then yields **2**.

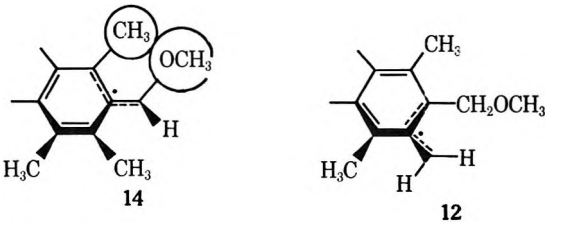


In the formation of tetramethylphthalyl bismethyl ether (**3**), initial abstraction of the most labile hydrogen (from $ArCH_2OMe$) could be followed by an intramolecular hydrogen transfer from the *o*-methyl group.[10] Subsequent oxygenation of the benzyl radical **12** and solvolysis of the intermediate hydroperoxide **13** would lead to the diether **3**.

The driving force for the 1,4 migration of hydrogen in the formation of **12** may be associated with the steric factors which bring about relatively less stabilization of the initially formed radical **14**. Thus, in **14**, the bulky methoxyl group may inhibit the achievement of coplanarity required for resonance stabilization of the radical by the aromatic ring as shown. The radical **12**, on the other hand, does not suffer from this



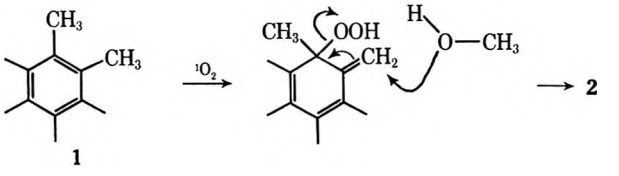
steric restriction[11] and orbital overlap with the ring is more easily accomplished. It is also worth noting that approach of oxygen to **12** appears to be less hindered than the approach to **14**.



An important point which needs clarification in considering the above sequences is the nature of the initial hydrogen abstraction step, or more generally, the pathway for hydroperoxide formation. A high-energy C–H bond scission resulting from the excited state of hexamethylbenzene can be ruled out since the energy of light used is low[12] and the methylene blue sensitizer is present in sufficient concentration to permit no primary light absorption by the hydrocarbon. The triplet energy (33 kcal/mol) of the sensitizer is not sufficient to populate the "radical like" Σ^1 state of oxygen, therefore eliminating this species as the hydrogen abstractor. It was also possbile to demonstrate that triplet oxygen alone is not involved in the hydrogen abstraction process. Thus, in a control reaction when the oxygenation was carried out in the absence of light and sensitizer by bubbling oxygen through a methanol–benzene solution of hexamethylbenzene for 10 days at 50°, only starting material was recovered. Based on the above considerations we suggest that the excited triplet state of the sensitizer, methylene blue, may be the agent affecting

(8) Surprisingly, no products of further oxidation were found when the bismethyl ether **3** was subjected to the photooxidation conditions for 9 days.

(9) Since it is known that singlet oxygen is generated under the conditions of the reaction, one may not rigorously exclude the possibility of an "ene" type singlet oxygen addition mechanism for the formation of **2**, involving hydroperoxide formation followed by reaction with solvent, as shown.



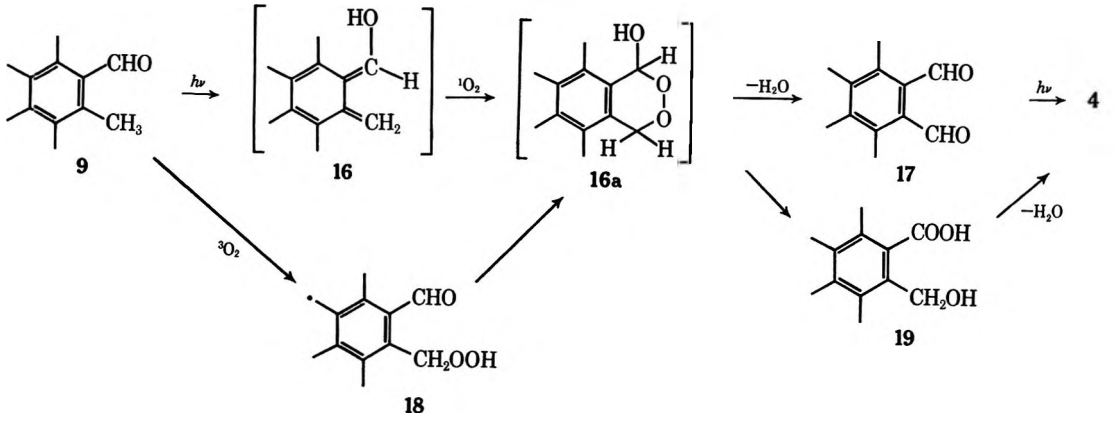
While there do not appear to be examples of the participation of an aromatic double bond in this type of oxygenation, it is conceivable that the extra crowding in hexamethylbenzene may render the system more susceptible to the ene reaction with singlet oxygen. In line with this view, we have observed that **1** undergoes photooxidation much more readily than either xylene or toluene. We thank a referee for drawing our attention to the above possibility.

(10) Radical isomerizations due to 1,4- and 1,5-hydrogen transfer reactions were first reported by A. Kossiakoff and F. Rice [*J. Amer. Chem. Soc.*, **65**, 590 (1943)] and more recently by V. B. Sefton and D. J. LeRoy, *Can. J. Chem.*, **34**, 41 (1956).

(11) L. Michaelis, M. P. Schubert, and S. Granick, *J. Amer. Chem. Soc.*, **61**, 1981 (1939), have found similar effects on the rates of radical cation (Würster salt) formation of various phenylene diamines due to steric factors.

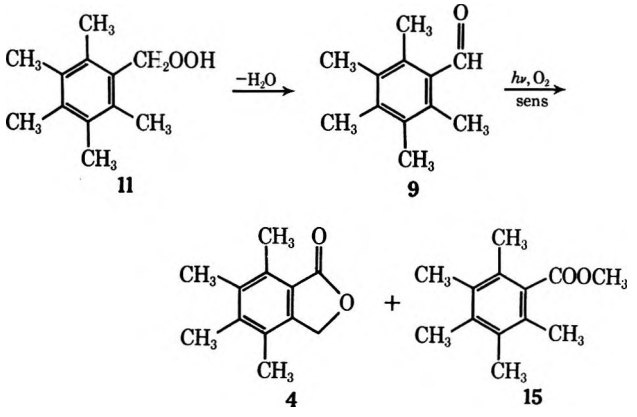
(12) Pyrex flasks were used so that light of wavelength lower than *ca.* 300 mμ is essentially filtered out.

SCHEME IV

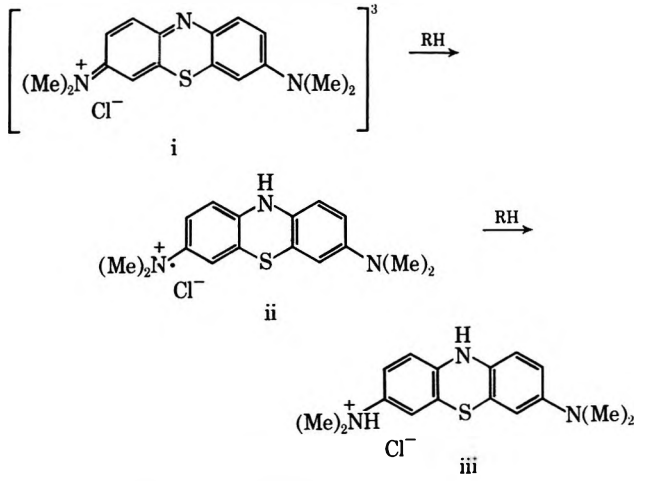


hydrogen abstraction.[13] This possibility has been proposed by Foote[4] and Matsuura[3] for related systems.

Reasonable pathways may be suggested for the production of tetramethylphthalide (**4**). One route involves a secondary photooxidation of the probable intermediate, pentamethylbenzaldehyde (**9**), formed by dehydration of the hydroperoxide **11**.



(13) Hydrogen abstraction by the triplet excited state of methylene blue (i) should be a favorable process,[4] since the radical cation formed (ii) would have a high degree of delocalization of the odd electron. Analogous systems, like the Würster salts, having a similar electronic and atomic constitution, are known to possess high stability. This rationale would also account for the efficient bleaching of methylene blue during the photooxidation of systems containing easily abstractable hydrogen atoms (1,4-cyclohexadiene and 1,4,5,8-tetralin), since transfer of a hydrogen atom to the radical cation (ii) would lead to the amine hydrochloride (iii).[14]



(14) Photobleaching of methylene blue by water has been studied by Y. Usui, H. Obata, and M. Koizumi, *Bull. Soc. Chem. Jap.*, **34**, 1049 (1961).

Precedent for this type of conversion of *o*-methylphenones to phthalides under conditions of photooxidation is found in the work of Yates and coworkers.[15] Along the lines of Yates' rationale (Scheme IV), photoenolization of **9** to **16** would be followed by uptake of oxygen (presumably in singlet form) to yield the transannular peroxide **16a** which could then decompose to the dialdehyde **17**, convertible on photolysis to **4**. In this connection we have observed that **9** may be photooxidized to a mixture of the tetramethylphthalide **4** (55%) and the ethyl ester **15** (38%) under the usual conditions employed in the above oxygenation reactions. On the other hand, one would not expect our conditions to favor the photoenolization of **9** to **16** since, in the region of irradiation (>300 mμ), almost all of the light (*ca.* >99%) would be absorbed by the methylene blue. Furthermore, energy transfer from methylene blue (E_t = 33 kcal/mol) to the benzaldehyde (E_3 = 72 kcal/mol) is unlikely. We therefore suggest that another process may be involved in the conversion of **9** to the hydroxy acid **19**. In this sequence, hydrogen abstraction from an *o*-methyl group leads to a radical which reacts with triplet oxygen to form the hydroperoxide **18**. Cyclization of **18** leads to **16a** which decomposes to the dialdehyde **17**. The latter, on further irradiation, rearranges to **4**. Alternatively, **16a** may break down to the hydroxy acid **19** which could then lactonize to **4**.

In the course of these studies we have noted a marked dependency of the oxidation reactions on the polarity of the medium. Thus, changes of solvent from methanol to methylene chloride resulted in a drastically reduced efficiency, whereby only 19% conversion to ethers **2** and **3** took place after 10 days, while only a trace of phthalide **4** was formed. By contrast, in 1:1 methanol–benzene, 93% conversion to products was observed. Similar diminished efficiency resulted when the methanol content of the solvent was reduced, although the ether to phthalide ratio remained the same. We are continuing our studies on these and related oxidation reactions in order to clarify the role of oxygen and solvent in the transformations.

Experimental Section

Photooxidation of Hexamethylbenzene.—Pure, dry oxygen was passed through a stirred, cooled (25°) solution of 1.000 g of

(15) P. Yates, A. C. MacKay, and F. X. Garmeaux, *Tetrahedron Lett.*, 5389 (1968); see also S. A. Pappar and J. E. Blackwell, *ibid.*, 3337 (1968).

hexamethylbenzene (Aldrich Chemical Co.) and 0.050 g of methylene blue in 700 ml of 1:1 methanol–benzene while irradiating with a 275-W sun lamp for 14 days. Concentration of the solution *in vacuo* gave an oil which was subjected to column chromatography on silica gel (Davison, grade 923, 100–200 mesh). Elution with benzene gave 0.116 g (11%) of recovered hexamethylbenzene.

Elution with 25% ether–benzene gave 0.368 g (31%) of a crystalline material, mp 65–67° (from 95% methanol), which was characterized as pentamethylbenzyl methyl ether on the basis of the following spectral and physical properties: nmr ($CDCl_3$) τ 5.50 (s, 3 H, methylene), 6.61 (s, 3 H, methoxyl), 7.68 (s, 6 H, *o*-methyls), 7.80 (s, 9 H, *m*- and *p*-methyls); ir (KBr) 3.54, 9.01 μ; mass spectrum *m/e* 192 (P), 176, 161 ($-OCH_3$), 160, 146 ($-CH_3OCH_3$). *Anal.* Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.98; H, 10.19.

Elution with 50% ether–benzene gave 0.499 g (37%) of a crystalline solid, mp 71–73° (from 95% methanol), which was characterized as tetramethylphthalyl bismethyl ether on the basis of the following spectral and physical properties: nmr ($CDCl_3$) τ 5.47 (s, 4 H, methylenes), 6.56 (s, 6 H, methoxyls), 7.69 (s, 6 H, *o*-methyls), 7.78 (s, 6 H, *m*-methyls); ir ($CHCl_3$) 3.55, 9.10 μ; mass spectrum *m/e* 222 (P), 190 ($-CH_3OH$), 165, 150, 137. *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.82; H, 10.22.

Elution with chloroform gave 0.087 g (8%) of a crystalline solid, mp 224–226° (from 95% methanol), which was characterized as tetramethylphthalide on the basis of the following spectral and physical properties: nmr ($CDCl_3$) τ 4.87 (s, 2 H, methylene), 7.35 (s, 3 H, *o*-methyl to C=O), 7.69 (s, 6 H, *o*-methyl and *p*-methyl to C=O), 7.78 (s, 3 H, methyl); ir (KBr) 5.75, 8.93, 9.86 μ; mass spectrum *m/e* 190 (P), 162 ($-CO$), 161, 133. *Anal.* Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.99; H, 7.76.

Irradiation, utilizing the above conditions, with the exception of shortening the time to 8 days, gave, after column chromatography, the following: recovered hexamethylbenzene, 0.049 g (5%); pentamethylbenzyl methyl ether, 0.913 g (78%); tetramethylphthalyl bismethyl ether, 0.184 g (11%).

Irradiation, utilizing the above conditions, with the exception of using a 100-W flood lamp for 16 days gave the following: pentamethylbenzyl methyl ether, 0.656 g (49%); tetramethylphthalyl bismethyl ether, 0.716 g (52%).

When the solvent for photooxidation was changed to 1:9 methanol–benzene, the product ratio after 8 days was as follows: recovered hexamethylbenzene, 0.834 g (83%); pentamethylbenzyl methyl ether, 0.165 g (14%); tetramethylphthalide, 0.029 g (1%).

Attempted Autoxidation of Hexamethylbenzene.—A solution of 0.50 g of hexamethylbenzene in 500 ml of 1:1 methanol–benzene was heated at 50° while pure, dry oxygen was passed through for 10 days. All light was rigorously excluded. Concentration *in vacuo* yielded a crystalline solid, shown by its spectral and physical properties to be unreacted hexamethylbenzene.

Photooxidation of Pentamethylbenzyl Methyl Ether (2).—Pure, dry oxygen was passed through a stirred, cooled (25°) solution of 1.750 g of pentamethylbenzyl methyl ether and 0.050 g of methylene blue in 700 ml of 1:1 methanol–benzene while irradiating with a 275-W sun lamp for 9 days. Concentration *in vacuo* gave an oil which was subjected to column chromatography on silical gel (Davison, grade 923, 100–200 mesh). Elution with 25% ether–benzene gave 1.605 g (86%) of tetramethylphthalyl bismethyl ether, characterized by its known spectral and physical properties (*vide supra*).

Photooxidation of Tetramethylphthalyl Bismethyl Ether (3).—Pure, dry oxygen was passed through a stirred, cooled (25°) solution of 0.300 g of tetramethylphthalyl bismethyl ether and 0.050 g of methylene blue while irradiating with a 250-W sun lamp for 9 days. Concentration of the solution *in vacuo* gave recovered, pure starting diether, mp 65–70°, with no traces of other products detectable by nmr, tlc, glc, or mass spectrum.

Photooxidation of Pentamethylbenzaldehyde (9).—Pure, dry oxygen was passed through a stirred, cooled solution of 100 mg of pentamethylbenzaldehyde (*vide infra* for preparation) and 50 mg of methylene blue in 200 ml of 1:1 methanol–benzene while irradiating with a 275-W sun lamp for 10 days. The solvent was removed *in vacuo* giving an oil which was subjected to preparative layer chromatography (2-mm silica gel plates) giving the following results. Cut 1 (R_f 0.75) gave 57 mg (38%) of an oil characterized as methyl pentamethylbenzoate by the following spectral properties: nmr ($CDCl_3$) τ 6.71 (s, 3 H, methoxyl), 7.83 s and 7.86 s (15 H, methyls); ir (CS_2) 3.40, 3.45, 5.82, 7.85, 9.07, 10.5, 13.6 μ; mass spectrum *m/e* 206 (P), 175 ($-CH_3O$), 154, 147 ($-CO_2CH_3$), 134, 119, 94. Cut 2 (R_f 0.35) gave 61 mg (55%) of a crystalline solid, mp 224–226°, the spectral properties of which were indistinguishable from those of tetramethylphthalide obtained above.

Pentamethylbenzyl Chloride (7).—To a stirred solution of 1.40 g of pentamethylbenzyl methyl ether in 20.0 ml of glacial acetic acid at 22° was added 5.0 ml of concentrated hydrochloric acid. A crystalline precipitate appeared instantaneously which was separated by filtration and dissolved in ether. The ethereal solution was washed with water, dried, and concentrated *in vacuo* giving a white crystalline solid. Recrystallization from hexane gave 1.32 g (93%) of pure pentamethylbenzyl chloride, mp 80–82°, which has the following spectral and physical properties: nmr ($CDCl_3$) τ 5.26 (s, 2 H, methylene), 7.63 (s, 6 H, *o*-methyls), 7.75 (s, 9 H, *m*- and *p*-methyls); ir (CS_2) 3.35, 3.43, 7.30, 7.30, 7.75, 7.93, 12.6, 13.5, 14.9 μ; mass spectrum *m/e* 198 and 196 (P), 162 and 160 ($-HCl$), 147 ($-CH_2Cl$), 130, 128. *Anal.* Calcd for $C_{12}H_{17}Cl$: C, 73.28; H, 8.71. Found: C, 73.23; H, 8.92.

Pentamethylbenzyl Alcohol (8).—A solution of 1.30 g of pentamethylbenzyl chloride and 3.00 g of silver nitrate in 50.0 ml of 50% aqueous acetone was stirred at 22° for 2.0 hr, after which time a voluminous white precipitate had formed. Ether was added and the ethereal layer separated by filtration, washed with water, dried, and concentrated *in vacuo* giving a crystalline white solid. Recrystallization from 1:1 benzene–hexane gave 0.95 g (79%) of pure pentamethylbenzyl alcohol, mp 162–163°, which has the following spectral and physical properties: nmr ($CDCl_3$) τ 5.28 (s, 2 H, methylene), 7.68 (s, 6 H, *o*-methyls), 7.78 (s, 9 H, *m*- and *p*-methyls), 8.46 (br s, 1 H, hydroxyl); ir ($CHCl_3$) 2.78, 2.92 br, 3.34, 3.44, 6.90, 7.25, 7.73, 9.07, 10.5, 10.9 μ; mass spectrum *m/e* 178 (P), 161 ($-OH$), 160 ($-H_2O$), 149, 147, 136, 134, 119, 105, 91. *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.63; H, 10.03.

Pentamethylbenzaldehyde (9).—A solution of 0.50 g of pentamethylbenzyl alcohol in 150 ml of dry benzene with 5.00 g of suspended, freshly prepared manganese dioxide was heated at 85° under nitrogen for 5.0 hr, cooled, and filtered through Celite. The resulting benzene solution was concentrated *in vacuo* giving a crystalline solid. Recrystallization from hexane gave 0.42 g (86%) of pure pentamethylbenzaldehyde, mp 148–150°, which has the following spectral and physical properties: nmr ($CDCl_3$) τ 0.60 (s, 1 H, aldehyde), 7.65 (s, 6 H, *o*-methyls), 7.80 (s, 3 H, *p*-methyl), 7.83 (s, 6 H, *m*-methyls); ir ($CHCl_3$) 3.33, 3.43, 3.64, 5.95, 6.20, 6.90, 7.22, 7.86, 9.28, 11.75 μ; mass spectrum *m/e* 176 (P), 175, 161 ($-CH_3$), 149, 147 ($-CHO$), 133, 119, 115, 105, 91. *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.55; H, 9.26.

Tetramethylphthalyl Dichloride (5).—Tetramethylphthalyl bismethyl ether (1.00 g) was treated under the same conditions described above for the monoether 2 to monochloride 7 conversion yielding, after recrystallization from hexane, 0.85 g (83%) of pure tetramethylphthalyl dichloride, mp 133–135°, which has the following spectral and physical properties: nmr ($CDCl_3$) τ 5.20 (s, 4 H, methylenes), 7.62 (s, 6 H, *o*-methyls), 7.75 (s, 6 H, *m*-methyls); ir ($CHCl_3$) 3.40, 6.45, 7.70, 8.00, 10.0, 10.5 μ; mass spectrum *m/e* 232 and 230 (P), 197, 196, and 195 ($-Cl$), 160 ($-2Cl$), 130, 115, 91. *Anal.* Calcd for $C_{12}H_{16}Cl_2$: C, 62.35; H, 6.98. Found: C, 62.10; H, 7.02.

Tetramethylphthalyldiol (6).—Tetramethylphthalyl dichloride (0.85 g) was reacted under same conditions described above for the monochloride 7 to monoalcohol 8 conversion yielding, after recrystallization from benzene, 0.76 g (93%) of pure tetramethylphthalyldiol, mp 173–175°, which has the following spectral and physical properties: nmr (acetone-d_6) τ 5.17 (s, 4 H, methylenes), 6.52 (br s, 2 H, hydroxyls), 7.64 (s, 6 H, *o*-methyls), 7.76 (s, 6 H, *m*-methyls); ir ($CHCl_3$) 2.79, 2.98 br, 3.35, 3.46, 6.15, 6.39, 7.76, 8.15, 9.39, 10.25, 10.50 μ; mass spectrum *m/e* 194 (P), 193, 175 ($-H_3O$), 160 ($-H_2O_2$), 146 132, 104, 90. *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.01.

Lithium Aluminum Hydride Reduction of Tetramethylphthalide.—To a suspension of 0.50 g of lithium aluminum hydride in 50.0 ml of anhydrous ether was added a solution of 0.05 g of tetramethylphthalide in 10.0 ml of anhydrous ether. After addition, the solution was stirred for 1.0 hr at 22° and quenched

with water. The ether layer was separated, dried, and concentrated *in vacuo* yielding a crystalline solid which after recrystallization from benzene gave 0.04 g of pure material, mp 171–173°, whose spectral and physical properties were indistinguishable from those of tetramethylphthalyldiol prepared by another route (*vide supra*).

Registry No.—2, 20145-50-0; 3, 29002-53-7; 4, 29002-54-8; 5, 29002-55-9; 6, 3205-92-3; 7, 484-65-1; 8, 484-66-2; 9, 17432-38-1; 15, 28195-45-1; hexamethylbenzene, 87-85-4.

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The Pschorr Reaction by Electrochemical Generation of Free Radicals. I. Phenanthrene Synthesis

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Contribution No. 530 from the Research Council of Alberta, Edmonton 7, Alberta, Canada

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Diazonium tetrafluoroborates of 2-amino-α-(R-phenyl)cinnamic acids have been reduced electrolytically at 0 V *vs.* sce and nonelectrolytically in aprotic solvents to produce substituted and nonsubstituted phenanthrene-10-carboxylic acids in near-quantitative yields. These cyclized products were produced by other methods in lower yields. The efficacy of a homolytic pathway through generation of phenyl σ radicals by a number of schemes is discussed.

Pschorr and Pschorr-like reactions have been the subject of numerous investigations since they were discovered by Graebe and Ullman[1] in 1894 and Pschorr[2] in 1896. These reactions are of importance not only as synthetic tools but from a mechanistic viewpoint as well. De Tar[3] and others[4–6] have pointed out that some of these reactions appear to proceed by a heterolytic and others by a homolytic pathway. We have recently developed a new route to intermolecular arylation by the electrochemical reduction of diazonium salts in aprotic solvents.[7] Since this method, as carried out in our laboratories, occurs under mild conditions, 0°, and goes by exclusively homolytic pathway, we decided to investigate two intramolecular reactions (*i.e.*, phenanthrene and fluorenone synthesis) to obtain improved yields and/or new information on mechanisms. How far we have succeeded with these objectives in cyclization to phenanthrene is the subject of this paper.

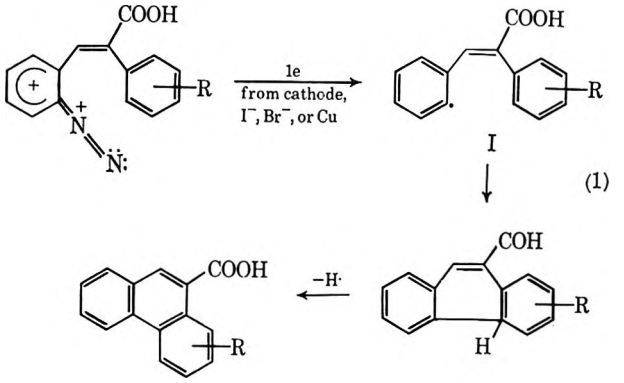
Results

The results of electrochemical reduction of diazonium salts of 2-amino-α-arylcinnamic acids are presented in Table I. For comparison, results of cyclizations of the same diazonium salts in aqueous fluoroboric acid (with and without copper) are included, as are results of one reduction of diazotized unsubstituted acid using iodide ion as the reducing agent, and, finally, results from other laboratories.

Yields from the electrochemical method were consistently high. Examination of products by melting points and infrared and mass spectral analysis gave no indication of by-products from such usual side reactions as replacement of the diazonium with hydrogen or fluoride ions. Substitution by hydroxyl group, not anticipated in an aprotic medium, was absent. Substituent effects on yields were insignificant within limits of experimental error incurred during isolation of products. The iodide ion cyclization also gave an excellent yield but about 10% of the by-product, 2-iodo-α-phenylcinnamic acid, was recovered. Replacing iodide with bromide gave high yields of cyclization comparable to the iodide reaction. The low (62%) yield obtained from cyclization by heating with aqueous fluoroboric acid was increased to 93% by the addition of copper powder.

Discussion

Intermolecular arylations by electrochemical reduction of benzenediazonium tetrafluoroborate in acetonitrile and monosubstituted benzenes produced considerable amounts of benzene (50–60%) due to abstraction of hydrogen atoms from the solvent.[7] No detectable hydrogen abstraction or dimerization occurred during intramolecular arylation of cinnamic acid derivatives, suggesting that conditions strongly favored cyclization (eq 1).



For the unstrained α-phenylcinnamic acid molecule, Hey and Mulley[8] have calculated the distance between positions to be linked by intramolecular bond formation to be 1.5 Å, and, hence, very favorable to cyclization. Since 1.5 Å applies only to the molecular configuration in which the rings are coplanar, the lifetimes of the

(1) C. Graebe and F. Ullmann, *Ber.*, **27**, 3483 (1894).
(2) R. Pschorr, *ibid.*, **29**, 496 (1896).
(3) D. F. De Tar, *Org. React.*, **9**, 409 (1957).
(4) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, London, 1960.
(5) R. Huisgen and R. E. Zahler, *Ber.*, **96**, 736 (1963).
(6) R. A. Abramovitch, *Advan. Free-Radical Chem.*, **2**, 87 (1966).
(7) F. F. Gadallah and R. M. Elofson, *J. Org. Chem.*, **34**, 3335 (1969).
(8) D. H. Hey and R. D. Mulley, *J. Chem. Soc.*, 2276 (1952).

TABLE I

PSCHORR CYCLIZATION OF DIAZONIUM SALTS OF 2-AMINO-α-ARYLCINNAMIC ACIDS UNDER DIFFERENT CONDITIONS

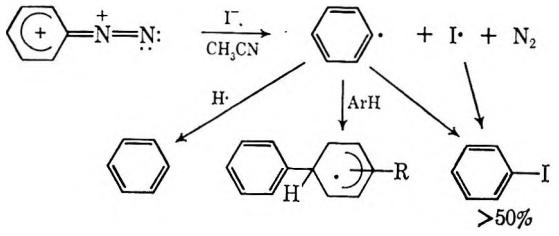
		Reaction conditions and yields, %						
R	Registry no.	Electrochemical reduction	H^+	H^+, Cu	$(CH_3)_2CO$, Cu	I^-	Br^-	Br^-, Hg
H	28987-33-9	95	62[a]	93[a]		85[b]	78[c]	82[c]
			60[d,e]	93[d,f,g]	81, 94[g,h]	70[i,j]		
4-CH_3	28987-34-0	90	20[d,e]	70[e,k]				
2-OCH_3	28987-35-1	80	55[d,l]					
3-OCH_3	28987-36-2	94[m]						
4-OCH_3	29038-90-2	93	50[d,l]					
2-Br	28987-37-3	94	60[n]					
4-Br	28987-32-8	96						

[a] Aqueous HBF_4 (10%). [b] CH_3CN, Pr_4NI. [c] CH_3CN, Pr_4NBr. [d] Aqueous H_2SO_4. [e] See ref 15. [f] See ref 2. [g] D. H. Hey and M. Osbond, *J. Chem. Soc.*, 3164 (1949). [h] See ref 8. [i] Aqueous H_2SO_4, $(CH_3)_2CO$, NaI. [j] B. Chauncy and E. Giullert, *Aust. J. Chem.*, 22, 993 (1969). [k] Aqueous HCl, EtOH. [l] See ref 17. [m] A mixture of 2- and 4-methoxyphenanthrenecarboxylic acids. [n] See ref 20.

free radical must be long relative to the time of oscillation or rotation of the rings.

In the normal course of a Pschorr phenanthrene synthesis, 60% yields can be obtained by simply heating the appropriate diazonium chloride or sulfate in dilute mineral acid. Addition of copper powder increases both the rate of reaction and the yield. Other workers have therefore concluded that these reactions probably proceed by some combination of heterolytic and homolytic mechanisms.[3-6]

In an attempt to assess the effect of the heterolytic pathway, the diazonium salt of 2-amino-α-phenylcinnamic acid was heated in 10% fluoroboric acid; 62% of cyclized product was obtained. When copper was added, a redox system capable of reducing the diazonium salt to a σ radical I resulted, giving a yield of 93%. A similar redox system could be produced with iodide ion in aprotic medium, which also gave high yields, but which was accompanied by the formation of about 10% of iodo-substituted acid. In intermolecular arylations, iodo substitution can be the major reaction, accounting for more than 50% of the products[9] (eq 2).



(2)

Some relevant redox potentials are listed in Table II. This tabulation shows why copper and copper salts facilitate replacement of diazonium groups by chlorine or bromine, though not by iodine, atoms not only in Pschorr reactions but in Sandmeyer and Meerwein reactions as well.

TABLE II

REDOX POTENTIALS *vs.* N HYDROGEN ELECTRODE[a,b]

$ArN_2 = ArN_2^+ + e$	$E_0 = -0.541$ V[c]
$I^- = {}^1/_2I_2 + e$	$= -0.536$ V
$CNS^- = {}^1/_2(CNS)_2 + e$	$= -0.77$ V
$Br^- = {}^1/_2Br_2 + e$	$= -1.066$ V
$Cl^- = {}^1/_2Cl_2 + e$	$= -1.360$ V
$F^- = {}^1/_2F_2 + e$	$= -2.85$ V
$Cu = Cu^+ + e$	$= -0.521$ V
$CuCl + Cl^- = Cu^+Cl_2 + e$	$= -0.538$ V
$CuBr + Br^- = Cu^+Br_2 + e$	$= -0.640$ V

[a] R. M. Elofson and F. F. Gadallah, *J. Org. Chem.*, **34**, 854 (1969). [b] W. M. Latimer, "Oxidation Potentials," 2nd ed, Prentice Hall, New York, N. Y., 1952. [c] From reversible $E_{1/2} = +0.295$ V *vs.* sce (ref 9).

(9) R. M. Elofson and F. F. Gadallah, unpublished results.

There is some error inherent in comparing potentials in acetonitrile with those determined in aqueous systems. For instance, benzenediazonium salts, $E_0 = -0.541$, are readily reduced by iodide in aprotic solvents, but the *N*,*N*-dimethylaminobenzenediazonium ion, $E_0 = -0.151$, is not reduced at all.

Bromide ion is apparently on the borderline of ions capable of reducing diazonium salts. In aprotic media diazonium salts of 2-amino-α-phenylcinnamic acid were reduced by bromide, giving high yields (*ca.* 82%) of cyclized products, but the reaction is very slow. Free bromine was produced. Bromine could be produced from bromide *via* one route only, *i.e.*

$$Br^- \xrightarrow{-e} Br\cdot \xrightarrow{Br\cdot} Br_2$$

Recently, Lewis and his coworkers[10] suggested that aqueous bromide participated in the decomposition of diazonium salts by a one-step mechanism (SN2). We now believe that the bromide ion with diazonium salts, in aprotic media at least, constitutes a redox system. The reaction proceeds some ten times faster in the presence of Hg^0 because mercury facilitates the one-electron transfer.[10a] The situation in aqueous and acidic systems is questioned in our laboratory, and investigations are in progress to be reported in subsequent publications.

Experimental Section

Reagents.—All reagents and solvents were purified by published methods.[7] Solid reagents and reference compounds were recrystallized and melting points agreed with literature values. Diazonium tetrafluoroborate salts were recrystallized from cold acetonitrile and ether and kept under high vacuum in the refrigerator. Gattermann copper powder[11] was prepared by adding zinc dust to a saturated aqueous solution of copper sulfate until the deep blue color started to change. The copper powder was filtered, washed with dilute HCl (four times), distilled water until test for chloride was negative, dry methanol, and dry ether, and then put under vacuum. Fluoroboric acid purified (48.5%)[12] and tetrabutylammonium perchlorate[13] were obtained commercially.

(10) E. S. Lewis, L. D. Hartung, and B. M. McKay, *J. Amer. Chem. Soc.*, **91**, 419 (1969).

(10a) NOTE ADDED IN PROOF.—Pyridine reduced the diazonium salt of 2-amino-α-phenylcinnamic acid (1:1 molar ratio in acetonitrile) and produced the cyclized compound in 84% yield: R. M. Elofson, F. F. Gadallah, and K. F. Schultz, *J. Org. Chem.*, **36**, 1526 (1971).

(11) C. Gattermann, *Ber.*, **2B**, 1219 (1890).

(12) J. T. Baker Chemical Co., Phillipsburg, N. J.

(13) Southwestern Analytical Chemicals, Inc., Austin, Texas.

General Procedure for the Preparation of 2-Amino-α-arylcinnamic Acids.—*o*-Nitrobenzaldehyde, arylacetic acid, acetic anhydride, and triethylamine were refluxed and cooled, and water was added.[14] The nitro compounds were reduced with H_2S and ammonia. Melting points and mass spectra verified the crystallized compounds.

General Procedure for the Electrolytic Reduction.—The apparatus has been described previously.[7] Tetrabutylammonium perchlorate, the electrolytic support,[7] was dissolved in acetonitrile to make a 0.1 *M* solution. This solution was used for both cathode and anode compartments. The diazonium salt was dissolved in the degassed and cooled solution in the cathode compartment to make 0.01 *M*. The reaction was run at 0 V *vs.* sce under purified nitrogen. A run was considered complete when the current dropped to less than 1 mA and the test for diazonium salt was negative. After completion, each reaction mixture was taken to dryness under vacuum at room temperature. The solid was extracted with ether (four times). The ether solution was dried and evaporated, the residue was dissolved in ammonium hydroxide solution (10%), precipitated with dilute hydrochloric acid, and filtered, and the precipitate was washed with water several times and dried by suction. Dissolving, precipitating, washing, and drying were repeated three times to remove tetrabutylammonium perchlorate. The vacuum-dried products were identified by melting points and infrared. Mass spectral analysis, in each case, gave the proper parent peak and fragmentations for the cyclized products only. The phenanthrene-10-carboxylic acid and its derivatives (R's) were crystallized from glacial acetic acid with a loss of *ca.* 5%; the melting points reported are uncorrected: phenanthrene-10-carboxylic acid, mp 256–257° (lit.[15] 250–252°); R, 3-OCH_3, mp 238–240° (lit.[16] 238–239°), R, 1-OCH_3, mp 218–220° (lit.[17] 215°); R, 2-OCH_3, mp 238° (lit.[18] 236.7°); R, 3-OCH_3, mp 240–241° (lit.[17] 239°); R, 3-Br, mp 285° (lit.[19] 290–291°); R, 1-Br, mp 296–297° (lit.[20] 295°).

Using Tetrapropylammonium Iodide for Reduction.—The diazonium salt was dissolved in dry, degassed acetonitrile at 0°. The solid iodide salt was added gradually with vigorous stirring under nitrogen. After 10 min sodium thiosulfate solution (2 g of $Na_2S_2O_3$/25 ml of water) was added and a precipitate formed. The precipitate was filtered, washed with water, and dried under vacuum to give pure phenanthrene-10-carboxylic acid (85%). The filtrate was concentrated, and ammonium hydroxide solution was added (10%) and filtered. The filtrate was acidified to give a precipitate which, after washing and drying, was identified as 2-iodo-α-phenylcinnamic acid (*ca.* 10%), mp 175–177° from ethyl acetate (lit.[21] 179–180°).

Using Tetrapropylammonium Bromide for Reduction.—Two sets of reactions were performed, one over a mercury pool and the other without mercury. The technique described for the iodide reaction was followed with no attempt to separate the 2-bromo-substituted products. At 0° the mercury reaction gave 82% phenanthrene-10-carboxylic acid in *ca.* 2.5 hr. The reaction without mercury was allowed to warm to room temperature overnight and gave 78% of cyclized product in *ca.* 22 hr. In both cases free bromine was produced.

Acid Reaction.—The diazonium salt was suspended in fluoroboric acid (10%) at room temperature with fast stirring. The temperature was raised gradually over 1 hr to 70° and kept at 70° for 10 min, at which time the test for the diazonium ion was negative. The reaction mixture was cooled and filtered. The solid was washed several times with water and then dried under vacuum. Fractional crystallization from glacial acetic acid gave the cyclized product (62%), 2-fluoro-α-phenylcinnamic acid (10%), mp 179° (lit.[22] 178°), 2-hydroxy-α-phenylcinnamic acid (3%), mp 198° (lit. 202–204°),[23] and 3-phenylcoumarin (~9%), mp 138.9°.

Acid and Copper Reaction.—The dry diazonium salt was added to a stirred suspension of copper in fluoroboric acid (10%). The reaction commenced at room temperature and the mixture was warmed to 70°. The cyclized products were isolated by the method described for the acid reaction.

(14) D. F. DeTar and Yun. Wen Chu, *J. Amer. Chem. Soc.*, **76**, 1686 (1954).
(15) R. Pschorr, H. Tappan, R. Hofmann, F. Quade, M. Schütz, and J. Popovici, *Ber.*, **39**, 3106 (1906).
(16) R. Pschorr, *ibid.*, **39**, 3112 (1906).
(17) R. Pschorr, O. Wolfes, and W. Buckow, *ibid.*, **33**, 162 (1900).
(18) C. K. Bradsher, F. C. Brown, and P. H. Leake, *J. Amer. Chem. Soc.*, **79**, 1471 (1957).
(19) R. Pschorr, *Ber.*, **39**, 3118 (1906).
(20) R. Pschorr, *Justus Liebigs Ann. Chem.*, **391**, 48 (1912).
(21) S. M. Kupchan and H. W. Wormser, *J. Org. Chem.*, **30**, 3792 (1965).
(22) K. Bowden and D. C. Parkin, *Can. J. Chem.*, **46**, 3909 (1968).
(23) N. R. Krishnaswamy, T. R. Seshadri, and B. R. Sharma, *Indian J. Chem.*, **2**, 182 (1964).

Electroorganic Chemistry. VII. Anodic Oxidation of Cyclopropanes

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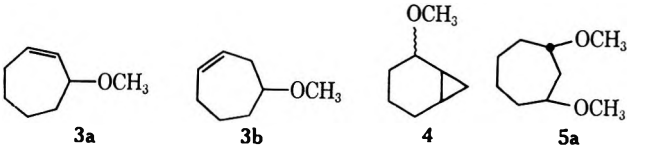
The electrochemical oxidation of bicyclo[4.1.0]heptane (1) and bicyclo[3.1.0]hexane (2) gave products in which the cyclopropane ring was opened. The structures or distributions of the products were completely different from those observed in the acidic solvolyses, metallic oxidations, and radical reactions of 1 and 2. It thus appeared that this electrochemical reaction was initiated by the direct oxidation of the carbon–carbon single bond of the cyclopropane ring. The bond cleavage was observed exclusively on the internal bond.

Synthetic reactions initiated by the anodic oxidation of the aromatic nucleus or aliphatic multiple bonds have been studied extensively,[1] while the electrochemical oxidations have never been studied on cyclopropanes in which the characters of the cyclopropane ring are considered to be similar, to a certain extent, to those of the olefinic bond. It was found in our laboratory that in the anodic oxidation of some arylcyclopropanes the aromatic nucleus rather than the cyclopropane ring was oxidized at the anode.[2] In the present study, we wish to report the first evidences that the carbon–carbon single bond in a cyclopropane ring could be anodically oxidized to yield ring-opened products which may be difficultly synthesized by the other methods.

(1) N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68**, 449 (1968).
(2) T. Shono and Y. Matsumura, *J. Org. Chem.*, **35**, 4157 (1970).

Results

Bicyclo[4.1.0]heptane (1) and bicyclo[3.1.0]hexane (2) were selected as the starting cyclopropyl compounds. In the preparative experiment, the methanolic solution of 1 was oxidized at room temperature using tetraethylammonium *p*-toluenesulfonate as a supporting electrolyte. A carbon rod was used as the electrode and 2 *F*/mol of electricity was passed. The analysis of the reaction products indicated the formation of compounds **3a**, **3b**, **4**, **5a**, **5b**, **6** and a small amount



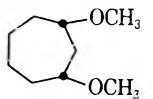
3a **3b** **4** **5a**

TABLE I

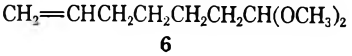
DISTRIBUTION OF PRODUCTS YIELDED IN THE ACIDIC SOLVOLYSIS OF 1

Condition	Products, %							Selectivity in bond cleavage, external/internal
								
Methanolysis, TsOH, 24 hr, reflux	26.6	10	4.6	50.6	8.2			87.2/12.8
Acetolysis,[a] TsOH, 24 hr, 47°	39.9	12.0	5.1	32.6	6.0	3.4	1.0	88.9/11.1
Acetolysis,[a] H_2SO_4, 41 hr, 46.5°	1.0	0.5	1.6	64.0	19.2	1.7	12.0	79.2/20.8

[a] Products are the corresponding acetate; see ref 8.



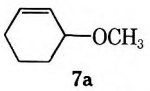
5b



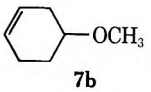
6

of unidentified product. Compounds **3a,b**, **4**, and **5a,b** were identified by the comparisons of their nmr spectra and gas chromatographic retention times with those of authentic samples synthesized independently.[3] Compound **6** was identified by its nmr spectrum and elemental analysis.

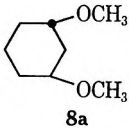
The oxidation of **2** in methanol gave compounds **7a**, **7b**, **8a**, **8b**, **9**, and a small amount of unidentified prod-



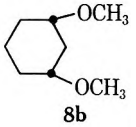
7a



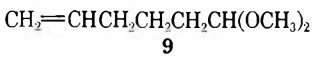
7b



8a



8b

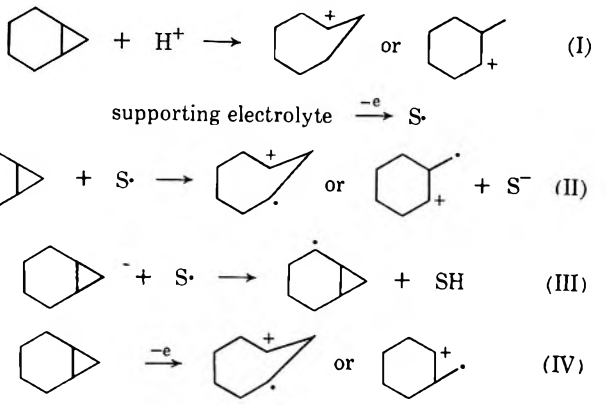


9

uct. The identification of the products were accomplished by the same methods as those used for compounds **3**, **4**, and **5**. The nmr data and elemental analysis of compound **9** supported the assigned structure. The compound corresponding to **4** was not detected in the oxidation products of **2**. All of the compounds **3**–**9** were the primary reaction products.

Possible Reaction Routes.—Although the products clearly indicated that the cyclopropane ring was opened under the anodic oxidation condition, it requires further evidences to establish that the reaction was initiated by the anodic oxidation of a carbon–carbon single bond in the cyclopropane ring.

The following four possible processes could be imagined for the initiation step. Process I, the attack of the proton which may be generated at the anode; process II, the oxidation of the cyclopropane ring by a certain oxidizing agent formed by the anodic oxidation of the supporting electrolyte or solvent; process III, the abstraction of a hydrogen from the substrate (**1** or **2**) by some radical species generated by the anodic oxidation; process IV, the electron transfer to the anode from a carbon–carbon single bond of the cyclopropane ring (direct anodic oxidation).



Methanolyses of 1 and 2.—Thus, the solvolytic reaction of **1** or **2** in methanol under acidic condition (catalyst, *p*-toluenesulfonic acid) was studied, and the results are indicated in Tables I and II along with some other reported data. The results indicated that the products obtained from the acidic solvolysis of **1** or **2** were completely different from those obtained in the anodic oxidation reaction.

Oxidations of 1 and 2 by Some Metal Acetates.—The reactions of **1** and **2** with some oxidizing agents such as lead tetraacetate or thallium triacetate have been studied by Ouellette and his collaborators.[4] The reported results are cited in Tables III and IV. Some of the products and their distributions were considerably different from the results observed in the anodic oxidation. Although a radical species generated from the supporting electrolyte or solvent by the anodic oxidation might behave as an oxidizing agent,[5] the oxidation of **1** or **2** by such an oxidizing agent would give considerably different products from those yielded in the present anodic oxidation. Furthermore, process II may be less probable since the oxidizing agent generated at a lower anode potential than that required for the direct oxidation of **1** or **2** must be incapable of oxidizing **1** or **2** and at the anode potential sufficiently anodic for the direct oxidation of **1** or **2**, process IV must become main reaction pathway.

Radical Reaction of 1.—It has been suggested in the anodic oxidation that a radical species yielded from the supporting electrolyte or solvent abstracts a hydrogen from substrates and the substrate radicals are anodically

(3) Compound **3a**, A. C. Cope, T. A. Liss, and G. W. Wood, *J. Amer. Chem. Soc.*, **79**, 6287 (1957); **3b**, A. C. Cope, S. Moon, and C. H. Park, *ibid.*, **84**, 4843 (1962); **4**, W. G. Dauben and W. T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967); **5a,b**, A. C. Cope, J. K. Heeren, and V. Seeman, *ibid.*, **28**, 516 (1963).

(4) R. J. Ouellette, A. South, Jr., and D. L. Shaw, *J. Amer. Chem. Soc.*, **87**, 2602 (1965).

(5) J. W. Britenbach and C. Srna, *Pure Appl. Chem.*, **4**, 245 (1962).

TABLE II

DISTRIBUTION OF PRODUCTS YIELDED IN THE ACIDIC SOLVOLYSIS OF 2

Condition	Products, % 						Selectivity in bond cleavage, external/internal
Methanolysis, TsOH, 26 hr, reflux	26.7	22.1	3.1	39.1	9.0		87.9/12.1
Acetolysis,[a] TsOH, 41 hr, 48[c]	3.1	10.1	8.8	53.0[b] 5.1[c]	17.2	2.3	74.0/26.0

[a] Products are the corresponding acetate; see ref 8. [b] Trans isomer. [c] Cis isomer.

TABLE III

DISTRIBUTION[a] OF PRODUCTS YIELDED BY THE OXIDATION OF 1

	3a	3b	4	5a	5b	10	6	Selectivity in bond cleavage, external/internal
Anodic oxidation, Et_4NOTs[b]	48.3		8.1	10.4	13.0	0	20.2	0/100
Anodic oxidation NaOMe[b]	23.4		35.2	10.2	11.0	0	20.2	0/100
Anodic oxidation at 1.3 V *vs.* sce, NaOMe[b]	0		100	0	0	0	0	
Kharasch reaction	Trace		*ca.* 100	0	0	0	0	
$Pb(OAc)_4$[c]	8.9	11.5	0	7.5	0	69.2	0	71/29
$Tl(OAc)_3$[c]	Trace	3.0	0	6.0	0	91.0	0	91/9

[a] The unidentified product was not included in the calculation of distribution. [b] Supporting electrolyte. [c] Products were the corresponding acetates; see ref 3.

TABLE IV

DISTRIBUTION[a] OF PRODUCTS YIELDED BY THE OXIDATION OF 2

	7a	7b	8a	8b	11	9	Selectivity in bond cleavage, external/internal
Anodic oxidation, Et_4NOTs[b]	23.1	24.0	15.2	19.5	0	18.2	0/100
$Pb(OAc)_4$[c]	24.0	27.0	Trace	24.5	24.5	0	24.5/75.5
$Tl(OAc)_3$[c]	19.6	24.9	3.4	5.6	46.5	0	46.5/53.5

[a] The unidentified product was not included in the calculation of distribution. [b] Supporting electrolyte. [c] Products were the corresponding acetates; see ref 3.

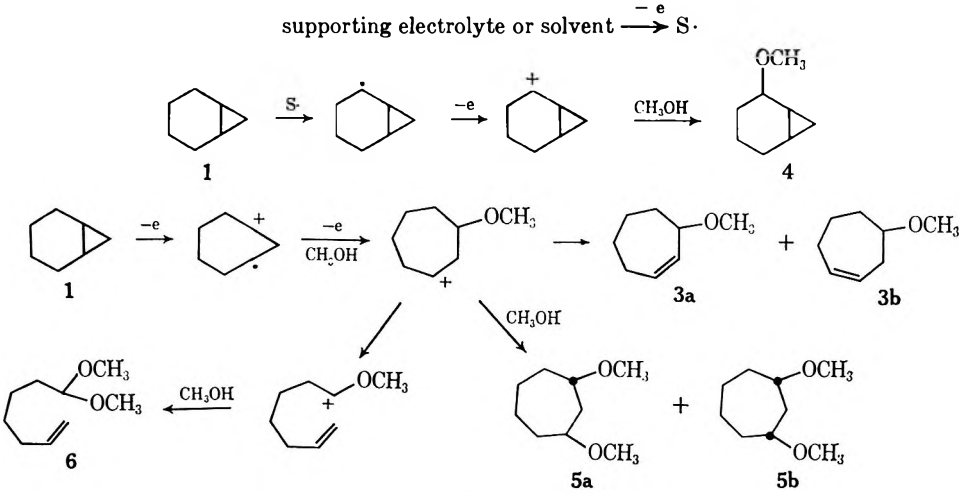
oxidized to cationic species.[6] This reaction process is mechanistically similar to the Kharasch reaction.[7] Thus, the behavior of **1** in the Kharasch reaction was studied and **4** was obtained as the exclusive product (Table III). Moreover, the controlled potential oxidation of **1** in methanol at 1.3 V *vs.* sce using sodium methoxide as a supporting electrolyte gave **4** exclusively (Table III). At the anode potential of 1.3 V *vs.* sce, the oxidation of the methoxide anion to the methoxy radical would be the only possible anodic process. It thus appeared that **4** was the product of the radical reaction initiated by process III, while **3a,b**, **5a,b**, and **6** were yielded by the other reaction pathway.

Reaction Route.—In the preparative anodic oxidation of **1**, the substitution of the supporting electrolyte of tetraethylammonium *p*-toluenesulfonate by sodium methoxide resulted in the increase in the formation of **4** (Table III). The oxidation potential of the former electrolyte is sufficiently higher than that of the latter. Thus, it would be concluded that the direct anodic oxidation of **1**, that is, the electron transfer to the anode from a carbon–carbon single bond of the cyclopropane ring of **1** (process IV), was the initiation process leading to the formation of **3a,b**, **5a,b**, and **6**. The reaction route of the anodic oxidation of **2** is similar to that of **1**. The reaction pathways are shown in Scheme I.

The remarkable characteristic of the anodic cyclopropane ring opening of **1** or **2** consisted of the high selectivity of the bond cleavage. The cyclopropane ring opening of **1** or **2** by the protonation, or **1** by the attack of an oxidizing agent, was observed almost at the external bond (Tables I–III). Furthermore, similar exclusive external bond cleavages were observed in the acidic solvolyses of *cis*- and *trans*-bicyclo[6.1.0]nonane and *cis*-bicyclo[5.1.0]octane.[8] The internal

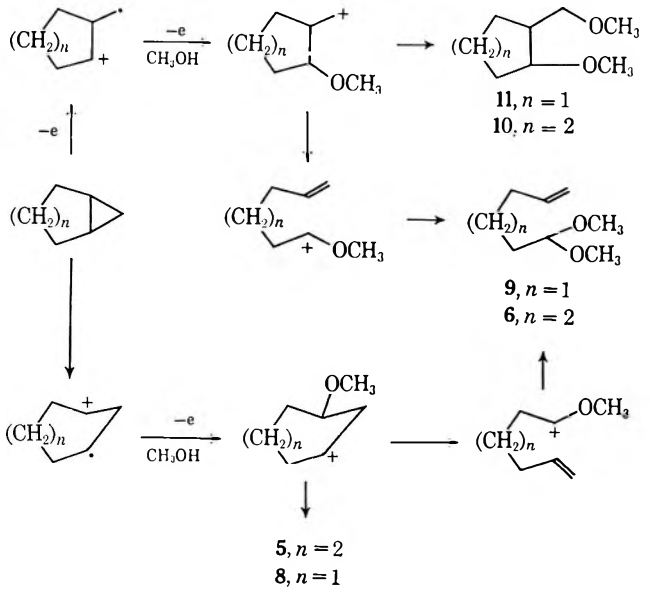
(6) T. Shono and T. Kosaka, *Tetrahedron Lett.*, 6207 (1968).
(7) C. Walling and A. A. Zavitsas, *J. Amer. Chem. Soc.*, **85**, 2084 (1963).
(8) K. B. Wiberg and A. deMeijere, *Tetrahedron Lett.*, 519 (1969).

SCHEME I



bond cleavages took place in the acidic solvolysis of highly strained compounds such as bicyclo[2.1.0]pentane[9] and *trans*-bicyclo[5.1.0]octane.[8] On the other hand, the anodic oxidation of **1** or **2** gave the products in which the bond cleaved was completely internal. Although the formation of **6** or **9** was explained by both external and internal routes, the lack of **10** or **11**[10] in the products make the external route less probable (Scheme II). The stereochemistry of the cleavage

SCHEME II



of the cyclopropane rings with electrophilic reagents is an attractive subject.[11,12] The nonstereoselective formation of compounds **5** and **8** in this anodic reaction suggests the carbonium ion character of the intermediate. The anodic oxidations of other polycyclic cyclopropyl systems and study on the reaction mechanism are in progress.

Experimental Section

Anodic Oxidation of Bicyclo[4.1.0]heptane (1). Supporting Electrolyte, Tetraethylammonium *p*-Toluenesulfonate.—In a 100-ml cylindrical cell, equipped with a reflux condenser and two carbon-rod electrodes (diameter, 0.8 cm) was placed a solution of 2.40 g (0.025 mol) of **1** and 0.75 g (0.0025 mol) of tetraethylammonium *p*-toluenesulfonate in 20 ml of methanol. The solution was stirred magnetically and electrolyzed at room temperature under the condition of constant current of 0.25 A until 2 *F*/mol of electricity was passed. The reaction mixture was poured into an excess of water and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate and distilled to remove ether. The residue was evaporated under reduced pressure and the distillate was trapped by a Dry Ice condenser. The gas chromatographic analysis (column, silicone DC 550) of the crude distillate [bp 70–96° (26 mm)] indicated that at least five compounds were contained in the products. Each compound was isolated by a preparative gas chromatograph (column, silicone DC 550), the total yield being 85.9%. Compounds **3a,b**, **4**, and **5a,b** were identified by the comparisons of their nmr spectra and gas chromatographic retention times (column, silicone DC 550, PEG 20M) with those of authentic samples synthesized independently.[3] Compound **6** was identified by its nmr spectrum and elemental analysis: nmr (CCl_4) τ 8.1 (m, 6, CH_2), 7.95 (m, 2, CH_2CH=), 6.8 (s, 6, OCH_3), 5.75 (t, 1, OCHO), 5.1 (m, 2, CH_2=), and 4.35 (m, 1, =CH).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.66; H, 11.78.

Sodium Methoxide as the Supporting Electrolyte.—A solution of 2.40 g (0.025 mol) of **1** and 0.135 g (0.0025 mol) of sodium methoxide in 30 ml of methanol was electrolyzed by the same method described above. The total yield of the products was 86.9%.

Controlled Potential Electrolysis.—A solution of 0.96 g (0.01 mol) of **1** and 0.54 g (0.01 mol) of sodium methoxide in 10 ml of methanol was electrolyzed under the condition of controlled anode potential of 1.3 V *vs.* sce until about 3 *F*/mol of electricity was passed. The reaction vessel employed was the same as that used in the constant current experiment, and the anode potential was controlled by Yanagimoto controlled potential electrolyzer VE-3. The gas chromatographic analysis (column, silicone DC 550, PEG 20M) indicated that compound **4** was the sole product.

Reaction of 1 with *tert*-Butyl Perbenzoate in the Existence of Copper Catalyst (Kharasch Reaction).—To a mixture of 4.8 g (0.05 mol) of **1**, 0.005 g of Cu_2Cl_2, and 0.64 g (0.02 mol) of methanol was added dropwise a solution of 1.94 g (0.01 mol) of *tert*-butyl perbenzoate in 1 ml of dry benzene. The reaction mixture was refluxed for 6 hr and extracted with ether. The ethereal solution was washed with a 2 *N* solution of sodium carbonate and analyzed by a gas chromatograph (column, silicone DC 550, PEG 20M) indicating that compound **4** (yield 7.5%) was the only product detectable by gas chromatography.

Acidic Methanolysis of 1.—A solution of 4.8 g (0.05 mol) of **1** and 1.9 g (0.01 mol) of *p*-toluenesulfonic acid in 20 ml of methanol was refluxed for 24 hr. Ether was added to the reaction mixture and the ethereal solution was washed with a 2 *N* solution of sodium carbonate. The comparisons of the gas chromatographic retention times (column, silicone DC 550, PEG 20M) with those of authentic samples indicated the existence of 1- and 3-methylcyclohexenes, cycloheptene, 1-methoxy-2-methylcyclohexane,

(9) R. T. Lalonde and L. S. Forney, *J. Amer. Chem. Soc.*, **85**, 3767 (1963).
(10) E. Buchta and H. Bayer, *Justus Liebigs Ann. Chem.*, **573**, 227 (1951).
(11) A. DeBoer and C. H. DePuy, *J. Amer. Chem. Soc.*, **92**, 4008 (1970).
(12) S. J. Cristol, W. Y. Lim, and A. R. Dahl, *ibid.*, **92**, 4013 (1970).

and cycloheptyl methyl ether in the ethereal solution. The total yield was 91.8%

Anodic Oxidation of Bicyclo[3.1.0]hexane (2).—The electrolysis of a solution of 8.2 g (0.1 mol) of 2 and 3.0 g (0.01 mol) of tetraethylammonium *p*-toluenesulfonate in 40 ml of methanol was carried out by the same method used in the anodic oxidation of 1. The gas chromatographic analysis indicated the formation of compounds **7a,b**, **8a,b**, and **9**, the total yield being 50%. The identifications of **7a,b** and **8a,b** were accomplished by the comparisons of their nmr data and gas chromatographic retention times with those of authentic samples. The nmr spectrum and elemental analysis of **9** coincided with the assigned structure: nmr (CCl_4) τ 8.5 (m, 4, CH_2), 7.95 (m, 2, CH_2CH=), 6.88 (s, 6, OCH_3), 5.73 (t, 1, OCHO), 5.05 (m, 2, =CH_2), and 4.35 (m, 1, CH=).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.68; H, 11.32.

Acidic Methanolysis of 2.—A solution of 2.1 g (0.025 mol) of bicyclo[3.1.0]hexane and 0.98 g (0.005 mol) of *p*-toluenesulfonic acid in 10 ml of methanol was refluxed for 26 hr. Work-up of the reaction mixture and product identification were carried out by the same method used in the methanolysis of 1. The total yield of products (Table II) was 90%.

Registry No.—**1**, 286-08-8; **2**, 285-58-5; **6**, 28995-68-8; **9**, 28995-69-9.

Acknowledgment.—The authors are grateful for the kind encouragement of Dr. Ryohei Oda.

Mechanism of the Diels–Alder Reaction of Halocyclopropenes[1a]

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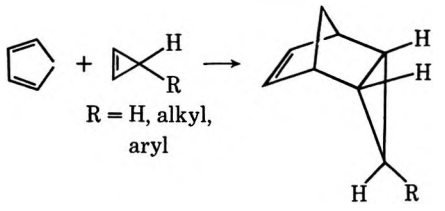
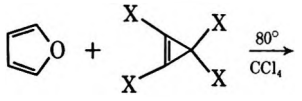
The possibility that perhalocyclopropenes undergo Diels–Alder reaction by first dissociating to a cyclopropenium halide ion pair which then reacts with diene is discussed. Several criteria for deciding between the one-step direct Diels–Alder mechanism and the two-step ionic process are described. Stereochemical studies and kinetic data (the order of the reaction, solvent polarity rate effects, activation parameters) appear to be consistent with the simple direct cycloaddition mechanism.

The great majority of cyclopropenes are excellent dienophiles in the Diels–Alder reaction, undergoing rapid cycloaddition with cyclopentadiene, for example, to produce the endo adduct;[2-4] monosubstitution at C_3 leads to formation of the endo–anti adduct[2a,b,d] and geminal disubstitution often inhibits reaction completely.[2a-d] This substituent effect has most reasonably been interpreted as being steric in origin.

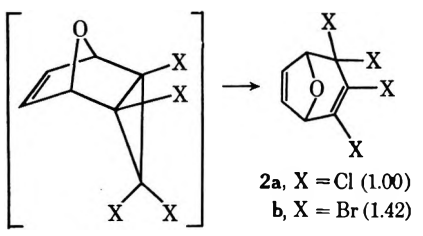


In contrast to these observations with alkyl- and aryl-substituted cyclopropenes, Law and Tobey[5] have argued that the Diels–Alder reactivity of perhalocyclopropenes, and the stereochemistry of their cycloadducts, has an electronic basis. Their study of the cycloadditions of six different perhalocyclopropenes with cyclopentadiene, furan, or butadiene revealed that all products have endo stereochemistry (or are derived from initial endo adducts by the cyclopropyl halide to allyl halide electrocyclic reaction[6]) and that the rate of cycloaddition to furan is greatest when the largest halogen (Br > Cl > F) is at C_3 of the starting material. Thus, relative to tetrachlorocyclopropene (**1a**), tetrabromocyclopropene (**1b**) reacts more rapidly, whereas all products from **3** and **6a–c** are formed more slowly (k_{rel} in parentheses).

Based upon these observations, Law and Tobey conclude (1) when the initially formed endo adduct has Br or Cl syn to the ethylene bridge, concerted ionization and disrotatory ring opening occurs[6] yielding the corresponding bicyclic diene (**2a,b**, **5**), and, when F is syn, the initial adduct is stable (**4**, **7a–c**); (2) since the rate of reaction increases as the C_3 substituent is changed from F to Cl to Br, neither the steric argument (above)



1a, X = Cl
b, X = Br



2a, X = Cl (1.00)
b, X = Br (1.42)

(1) (a) Partial support of this work by the Robert A. Welch Foundation is gratefully acknowledged, as is the assistance of the National Science Foundation in the purchase of a Varian Associates A-56/60A nmr spectrometer. (b) To whom inquiries should be addressed at the Department of Chemistry, The University of Tennessee, Knoxville, Tenn. 37916. (c) National Defense Education Act Fellow, 1966–1969.

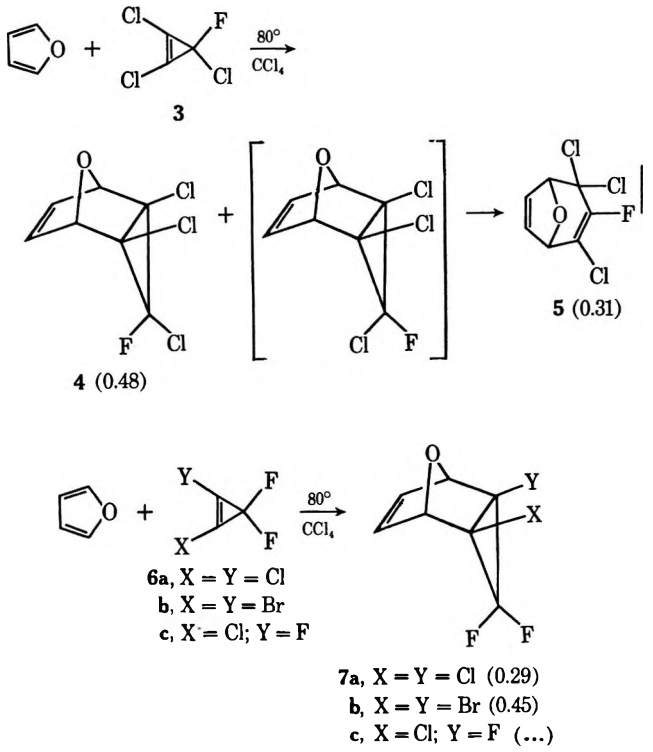
(2) (a) G. L. Closs, *Advan. Alicycl. Chem.*, **1**, 53 (1966); (b) G. L. Closs, L. E. Closs, and W. A. Böll, *J. Amer. Chem. Soc.*, **85**, 3796 (1963); (c) J. A. Berson and M. Pomerantz, *ibid.*, **86**, 3896 (1964); (d) M. A. Battiste, *Tetrahedron Lett.*, 3795 (1964); (e) S. C. Clarke, K. J. Frayne, and B. L. Johnson, *Tetrahedron*, **25**, 1265 (1969); (f) J. S. Haywood-Farmer and R. E. Pincock, *J. Amer. Chem. Soc.*, **91**, 3020 (1969).

(3) Some examples of exo addition have recently been reported,[4] most of them involving dienes like cyclopentadienones and furans for which nonbonded interactions in the exo transition state are less severe than with cyclopentadiene.

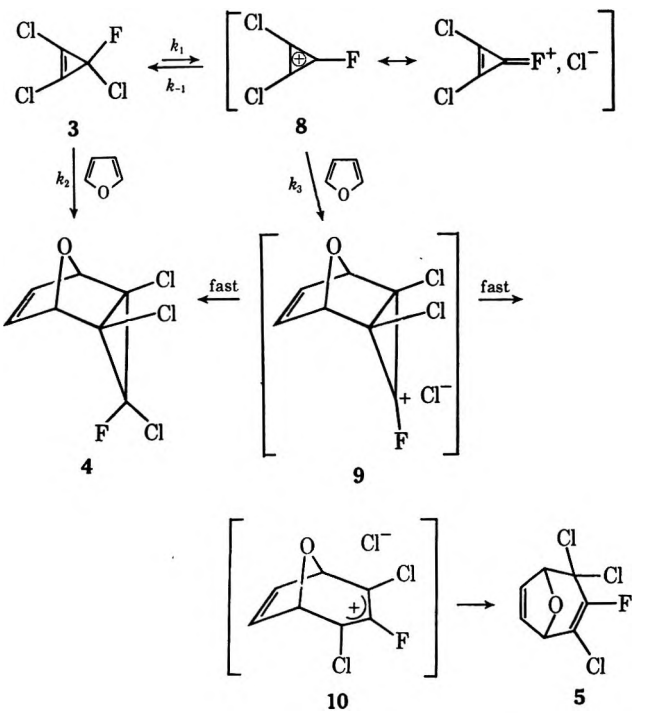
(4) (a) R. Breslow and J. T. Groves, *J. Amer. Chem. Soc.*, **92**, 984 (1970); (b) R. Breslow, G. Ryan, and J. T. Groves, *ibid.*, **92**, 988 (1970); (c) P. B. Sargeant, *ibid.*, **91**, 3061 (1969); (d) H. Monti and M. Bertrand, *Tetrahedron Lett.*, 2587, 2591 (1970); (e) J. P. Zahra and B. Waegell, *ibid.*, 2537 (1970); (f) M. A. Battiste and C. T. Sprouse, Jr., *ibid.*, 3165, 3893 (1969); (g) D. T. Longone and D. M. Stehouwer, *ibid.*, 1017 (1970).

(5) D. C. F. Law and S. W. Tobey, *J. Amer. Chem. Soc.*, **90**, 2376 (1968).

(6) See the following recent papers and references cited therein: (a) U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **7**, 588 (1968); (b) P. v. R. Schleyer, T. M. Su, M. Saunders, and J. C. Rosenfeld, *J. Amer. Chem. Soc.*, **91**, 5174 (1969); (c) T. M. Su, W. F. Sliwinski, and P. v. R. Schleyer, *ibid.*, **91**, 5386 (1969); (d) J. M. Bollinger, J. M. Brinich, and G. A. Olah, *ibid.*, **92**, 4025 (1970); (e) D. T. Clark and G. Smale, *Chem. Commun.*, 868, 1050 (1969); (f) W. E. Parham and K. S. Yong, *J. Org. Chem.*, **35**, 683 (1970).



SCHEME I



nor the Alder rule for dienophile reactivity appears to be operative; an argument based upon stabilization of the ground-state reactant (F > Cl > Br) is suggested.

There is another explanation, however, that is consistent not only with these rate and product studies but also with the steric effect expected for a C_3 halogen. This alternate mechanism is based upon a prior ionization of the cyclopropene followed by cycloaddition of the resulting ion pair with diene,[7] shown in Scheme I for the reaction of 1,2,3-trichloro-3-fluorocyclopropene (**3**) with furan.

In support of this scheme are the following considerations.

(1) Any *direct* Diels–Alder reaction (k_2) should produce only **4**, consistent with the smaller steric demands of F.

(2) Adduct **4** may be formed, in part, *via* cycloaddition of ion pair **8**, but this should not be a major route since 3,3-difluorocyclopropenes (**6a–c**) readily give adduct but are unlikely to ionize.

(3) The postulated equilibrium between covalent compound **3** and ion pair **8** is a well-established and facile process for 3-chlorocyclopropenes in a variety of solvents;[4a,b] the equilibrium should lie far to the left.

(4) The cationic moiety of the ion pair is stablized by fluorine, perhaps by the contributing structure having positive charge on the halogen.[4a,b,11] Because of this and because of the greater leaving-group ability of Cl relative to F, ion pair **8**, alone, is formed.

(5) Partial localization of the π electrons[11e] as implied by the second contributing structure serves to guarantee that cycloaddition will occur exclusively across the vic dichloro substituted bond; ion-pair return to **3** rather than its gem dichloro isomer is well established.[11e]

(6) Cycloaddition of a cyclopropenium ion with a diene is a thermally allowed process[12] and should occur on the face of the three-membered ring anti to the gegenion. By analogy to the reaction of other cyclopropenes, endo cycloadduct **9** is shown; analogy to the [4 + 2] cycloaddition of dienes with allylic cations,[13] however, might suggest that exo adduct would be favored. Although the overall conversion of a cyclopropenium ion into an allylic cation should be endothermic by nearly 20 kcal/mol,[4a] the process is made feasible here by the exothermic formation of two σ bonds.

(7) Ionic cycloadduct **9** can either collapse to **4** (which is stable because of the reluctance of F to ionize in the recognized disrotatory mode[6]) or, because there are no restrictions on the disrotatory opening of an already formed cyclopropyl cation, can yield allylic cation **10** which collapses to **5**.

(8) Generalizing from this scheme, *gem*-difluorocyclopropenes **6a–c** react exclusively by the single-step mechanism (k_2) because of the low steric requirement coupled with poor leaving-group ability. Conversely, *gem*-dibromo- and *gem*-dichlorocyclopropenes **1b** and **1a** undergo the two-step process (k_3), exclusively, the

(7) A similar multistep ionic scheme has been advanced for the cycloaddition reactions of cyclopropanones,[8] aziridines,[9] and epoxides.[10]

(8) (a) S. S. Edelson and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 2770 (1970); (b) N. J. Turro, S. S. Edelson, and R. B. Gagosian, *J. Org. Chem.*, **35**, 2058 (1970).

(9) (a) R. Huisgen, W. Scheer, and H. Mäder, *Angew. Chem., Int. Ed. Engl.*, **8**, 602 (1969); (b) R. Huisgen, W. Scheer, H. Mäder, and E. Brunn, *ibid.*, **8**, 604 (1969); (c) R. Huisgen and H. Mäder, *ibid.*, **8**, 604 (1969); (d) P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, **35**, 888 (1970).

(10) (a) T. Do-Minh, A. M. Trozzolo, and G. W. Griffin, *J. Amer. Chem. Soc.*, **92**, 1402 (1970); (b) D. R. Arnold and L. A. Karnischky, *ibid.*, **92**, 1404 (1970); (c) W. F. Bayne and E. I. Snyder, *Tetrahedron Lett.*, 2263 (1970).

(11) (a) R. West, A. Sâdo, and S. W. Tobey, *J. Amer. Chem. Soc.*, **88**, 2488 (1966); (b) R. West, *Accounts Chem. Res.*, **3**, 130 (1970); (c) R. M. Smith and R. West, *Tetrahedron Lett.*, 2141 (1969); (d) M. A. Battiste and B. Halton, *Chem. Commun.*, 1368 (1968); (e) D. J. Burton and G. C. Briney, *J. Org. Chem.*, **35**, 3036 (1970).

(12) For a discussion of cycloaddition reactions of aromatic compounds, see D. Bryce-Smith, *Chem. Commun.*, 806 (1969).

(13) (a) H. M. R. Hoffmann, D. R. Joy, and A. K. Suter, *J. Chem. Soc. B*, 57 (1968); (b) H. M. R. Hoffmann and D. R. Joy, *ibid.*, 1182 (1968).

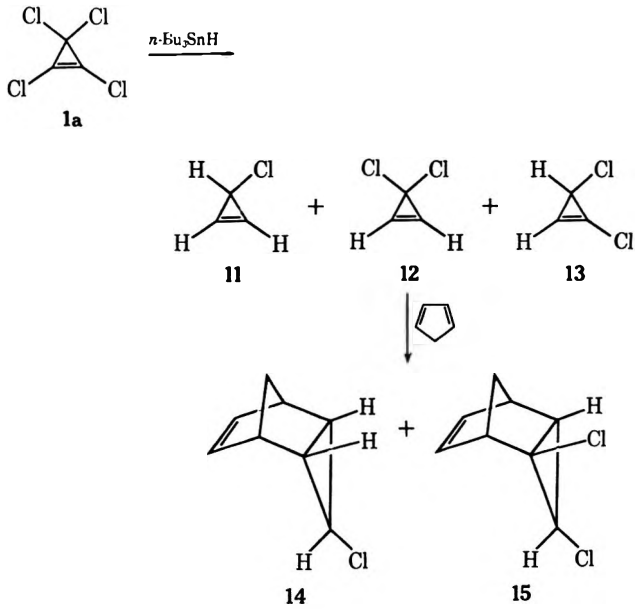
faster reaction of **1b** being due to its more ready bond heterolysis.

A number of approaches may be used to probe for the validity of the two-step mechanism. Several of these are described in the following section.

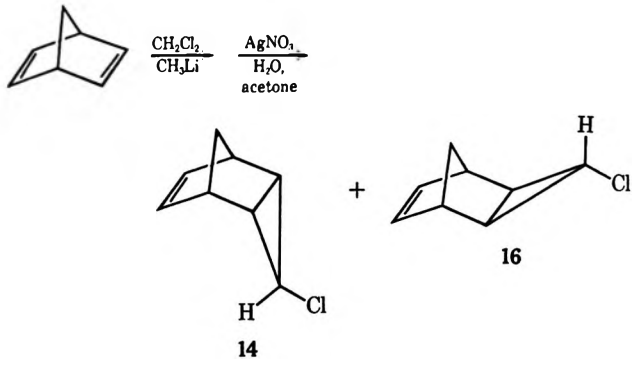
Results and Discussion

Our initial studies focused on a possible stereochemical distinction between the one-step and two-step mechanisms. The accumulated data from the cyclopropene literature strongly support the contention that direct Diels–Alder reaction (k_2) of perhalocyclopropenes with cyclopentadiene will lead to endo product.[2] On the other hand, a firm prediction of product stereochemistry in the two-step ionic mechanism is more difficult to make; as was discussed earlier, analogy to the known [4 + 2] chemistry of allylic cations[13] would suggest exo adduct as a distinct possibility. Whether exo or endo adduct is initially formed is a moot question for cyclopropenes **1a** and **1b** since only ring-opened products **2a** and **2b** are produced. We considered the possibility of trapping the initial cyclopropyl adduct by reductive removal of the halogens but were unable to find conditions suitable for this task.

We therefore turned to an investigation of adduct stereochemistry from less highly halogenated cyclopropenes for which the initially formed cyclopropanes are stable. Following the procedure of Breslow, *et al.*,[4b] reduction of tetrachlorocyclopropene (**1a**) with tri-*n*-butyltin hydride in paraffin oil affords a mixture consisting of 59% 3-chlorocyclopropene (**11**), 14% 3,3-dichlorocyclopropene (**12**), and 27% 1,3-dichlorocyclopropene (**13**). Reaction of this mixture with an excess of cyclopentadiene in CCl_4 at room temperature produces two adducts, **14** and **15**, whose endo structures and additional stereochemistry can be rigorously assigned. There is no evidence for the formation of any exo adduct.

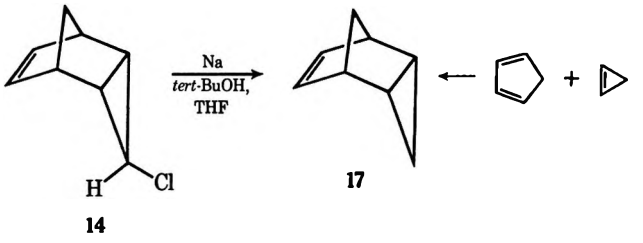


Adduct **14** is identical with the minor product (26%) formed by reaction of chlorocarbenoid with norbornadiene, followed by treatment with aqueous silver nitrate to remove any allylic chlorides; the major product (74%) from this reaction is the exo isomer **16**.[14]



Structures **14**, **15**, and **16** are strongly supported by nmr data on these compounds (see Experimental Section for the complete spectra). Briefly, endo–anti structure **14** is suggested by the small coupling constant of the proton on the chlorine-bearing carbon (J = 1.5 Hz),[2a,14,15a] by its relatively high chemical shift (δ 2.48),[2d] by the relatively high chemical shift of the vinyl protons (δ 5.85),[2e] and by the nearly identical chemical shifts of the two methylene protons (*ca.* δ 1.7).[14a,15b] The exo–anti structure **16** is suggested by the small coupling constant (J = 1.5 Hz) but relatively low chemical shift (δ 3.68) of the proton on the chlorine-bearing carbon, by the relatively low chemical shift of the vinyl protons (δ 6.45), and by the nonequivalence and upfield shift of the two methylene protons (δ *ca.* 0.8 and 1.1). Similar arguments lead to the endo–anti structure **15** for the dichloro compound.

Chemical confirmation of the endo stereochemistry of **14** is obtained from its reduction by sodium in *tert*-butyl alcohol[16] to the known tricyclic olefin **17**, the Diels–Alder adduct of cyclopropene and cyclopentadiene.[2a,17]



Thus, both mono- and dichlorocyclopropenes **11** and **13** yield endo adducts exclusively, a result allowed by either the one-step or two-step mechanisms. It should be noted that, according to our general formulation of the ionic mechanism, it is not unreasonable to expect **11** and **13** to react entirely by direct Diels–Alder reaction since intervention of the ionic mechanism is predicated upon there being severe steric interactions in the one-step cycloaddition of 3,3-dihalocyclopropenes. We therefore decided to concentrate all of our efforts on

(14) In general, carbene additions to norbornenes and related compounds preferentially give exo product: (a) C. W. Jefford and W. Wojnarowski, *Tetrahedron*, **25**, 2089 (1969); (b) C. W. Jefford and D. T. Hill, *Tetrahedron Lett.*, 1957 (1969), and references cited therein.

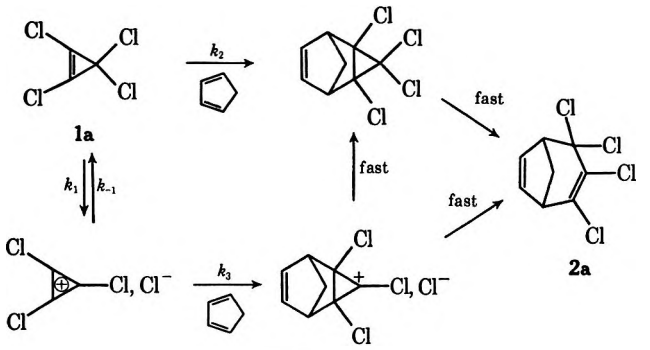
(15) (a) C. W. Jefford, E. H. Yen, and R. Medary, *ibid.*, 6317 (1966); (b) C. W. Jefford and R. T. Medary, *Tetrahedron*, **23**, 4123 (1967).

(16) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964).

(17) K. B. Wiberg and W. J. Bartley, *J. Amer. Chem. Soc.*, **82**, 6375 (1960).

securing meaningful mechanistic data for tetrachlorocyclopropene (**1a**).

Depending upon the relative magnitudes of the rate constants, investigation of the kinetics of the cycloaddition could reveal which mechanism is operative. Under pseudo-first-order conditions (large excess of cyclopentadiene), the rate expression for the direct Diels–Alder reaction is given by eq 1 and the observed rate constant by eq 2. By application of steady-state principles, the rate law for the two-step mechanism is again given by eq 1 but the observed rate constant by eq 3.



$$\frac{d[2a]}{dt} = k_{obsd}[1a] \quad (1)$$

$$k_{obsd} = k_2[\text{diene}] \quad (2)$$

$$k_{obsd} = \frac{k_1 k_3[\text{diene}]}{k_{-1} + k_3[\text{diene}]} \quad (3)$$

For the two-step mechanism (eq 3), three possibilities exist. (a) k_1 is rate determining, in which case the reaction rate is independent of diene concentration ($k_{obsd} = k_1$). (b) k_3 is rate determining, in which case the kinetics cannot distinguish between the one-step and two-step processes ($k_{obsd} = k_1k_3[\text{diene}]/k_{-1}$). (c) k_{-1} and $k_3[\text{diene}]$ are of comparable magnitude, in which case a plot of the observed pseudo-first-order rate constant *vs.* [diene] increases linearly at low concentrations but bends and approaches k_1 asymptotically at high concentrations $\{k_{obsd} = k_1k_3[\text{diene}]/(k_{-1} + k_3[\text{diene}])\}$.

Thus, unless condition b arises, the ion-pair mechanism is kinetically distinguishable from the direct cycloaddition. Even if b persists for a given diene, changing to a more reactive diene could alter the relative magnitudes of k_{-1} and $k_3[\text{diene}]$ (the rates of the reverse and forward reactions of the ion pair) such that condition c is achieved.

In addition, the rate of the two-step mechanism should be substantially more sensitive to changes in solvent polarity than should that of the direct Diels–Alder reaction.[18] At one extreme, condition a, a clear increase in rate with increasing solvent polarity should be observed. Even at the other extreme, condition b, the rate should be sensitive to solvent polarity; although k_3 will not vary appreciably, k_1/k_{-1} (the equilibrium constant for ion-pair formation) should show a marked solvent dependence.[4a,b]

Reaction of tetrachlorocyclopropene (**1a**) with a 20-fold excess of cyclopentadiene in a variety of solvents produces adduct **2a** as the only product (>95% isolated yields in all cases). The rate of product formation is conveniently monitored by quantitative glpc analysis (internal standard method). In every solvent system investigated, the kinetics are cleanly pseudo-first-order. The second-order rate constants, k, in Table I are obtained by dividing k_{obsd} by [diene].

TABLE I
RATE CONSTANTS FOR THE REACTION OF TETRACHLOROCYCLOPROPENE WITH CYCLOPENTADIENE IN VARIOUS SOLVENTS

Solvent	E_T[a]	Temp, °C	$k \times 10^5$,[b] l. mol^{-1} sec^{-1}
Carbon tetrachloride	32.5	25	0.83
Benzene	34.5	25	1.6
Acetone	42.2	25	2.0
Acetone	42.2	47	6.8
N,*N*-Dimethylformamide	43.8	25	2.7

[a] K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, *Justus Liebigs Ann. Chem.*, 661, 1 (1963). [b] Calculated by dividing the pseudo-first-order rate constant k_{obsd} by [cyclopentadiene].

There is only a small increase in rate with increasing solvent polarity, comparable to the increase observed in other cycloadditions.[18] Furthermore, doubling the concentration of diene in either benzene or acetone exactly doubles k_{obsd} (*i.e.*, the second-order rate constant, k, of Table I is unchanged). From the rates at two temperatures in acetone, one calculates $\Delta H^{\ddagger} = 10$ kcal/mol and $\Delta S^{\ddagger} = -44$ eu, normal values for a Diels–Alder reaction.[18]

Several attempts were made to determine if the reaction could be catalyzed by Lewis acids, as would be expected for the two-step mechanism. Although most metal halides lead to polymerization of the diene, mercuric chloride does not. Nevertheless, the presence of as much as 1 equiv of $HgCl_2$ in THF has no effect on the rate.

Thus, for cyclopentadiene as the 4-π-electron component, the evidence favors a normal Diels–Alder reaction on the covalent starting material **1a**.

Experimental Section

Instruments.—Analytical glpc was performed on a Perkin-Elmer Model 800 gas chromatograph (flame ionization detector) and utilized the following columns: A, 3 ft × 1/8 in., SE-30 (15%) on Chromosorb P; B, 6 ft × 1/8 in., Carbowax 20M (10%) on Chromosorb P. Quantitative glpc analyses employed the internal standard method; peak areas were measured with a Disc integrator. Preparative glpc was performed on a Varian Aerograph Model 202-1B gas chromatograph (thermal conductivity detector) and utilized the following columns: C, 20 ft × 3/8 in., SE-30 (30%) on Chromosorb P; D, 3 ft × 3/8 in., Carbowax 20M (10%) on Chromosorb W. All nmr spectra were obtained on a Varian Associates A-56/60A spectrometer.

Materials.—Tetrahydrofuran (THF) from Matheson Coleman and Bell was distilled from $LiAlH_4$ and stored over Na ribbon or molecular sieves. *N*,*N*-Dimethylformamide (DMF) from Matheson Coleman and Bell was dried over molecular sieves. Thiophene-free benzene, J. T. Baker Chemical Co., was dried over Na ribbon. Acetone and CCl_4, both ACS reagents from Allied Chemical Co., were used directly without purification. Norbornadiene (Eastman Organic Chemicals), *tert*-butyl alcohol (Matheson Coleman and Bell), $LiAlH_4$ and CH_3Li(LiBr) (both from Alfa Inorganics, Inc.), tri-*n*-butyltin chloride (Aldrich Chemical Co., Inc.), and trichloroacetic acid (Fisher Scientific Co.) were all used directly without further purification.

Cyclopentadiene was obtained by distillation from dicyclopentadiene (Aldrich Chemical Co.). Tri-*n*-butyltin hydride was

(18) (a) S. Seltzer, *Advan. Alicycl. Chem.*, **2**, 1 (1968); (b) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967); (c) J. E. Baldwin and J. A. Kapecki, *J. Amer. Chem. Soc.*, **92**, 4868 (1970); (d) M. J. S. Dewar and R. S. Pyron, *ibid.*, **92**, 3098 (1970).

prepared by $LiAlH_4$ reduction of tri-*n*-butyltin chloride.[19] Pentachlorocyclopropane was obtained from the reaction of dichlorocarbene with trichloroethylene[20a] and was converted into tetrachlorocyclopropene (**1a**) by established procedures.[20b] Reduction of tetrachlorocyclopropene with tri-*n*-butyltin hydride, according to the method of Breslow, *et al.*,[4b] yielded a mixture of 3-chlorocyclopropene (**11**), 3,3-dichlorocyclopropene (**12**), and 1,3-dichlorocyclopropene (**13**).

Reaction of Cyclopentadiene with 3-Chlorocyclopropene (11), 3,3-Dichlorocyclopropene (12), and 1,3-Dichlorocyclopropene (13).—To 0.6 g of a mixture consisting of 59% **11**, 14% **12**, and 27% **13** in 5 ml of CCl_4 at room temperature was added 2 ml of freshly distilled cyclopentadiene. After the exothermic reaction had subsided, most of the solvent and cyclopentadiene was removed with a rotatory evaporator. Glpc analysis (column B) revealed the presence of two major products and a number of very minor ones. Preparative glpc (column D) led to isolation of the two products which were identified as *endo,anti*-3-chlorotricyclo[3.2.1.$0^{2,4}$]oct-6-ene (**14**) [nmr (CCl_4) δ *ca.* 1.7 (m, 2, H_8), *ca.* 1.8 (m, 2, H_2, H_4), 2.48 (t, 1, J = 1.5 Hz, H_3), 3.03 (m, 2, H_1,H_5), and 5.85 (t, 2, J = 2 Hz, H_6,H_7)] and *endo,anti*-2,3-dichlorotricyclo[3.2.1.$0^{2,4}$]oct-6-ene (**15**) [nmr (CCl_4) δ 1.81 (m, 2, H_8), 2.20 (m, 1, H_4), 2.95 (d, 1, J = 2.5 Hz, H_3), 3.19 (m, 2, H_1,H_5), and 6.01 (m, 2, H_6,H_7)].

Reaction of Norbornadiene with Chlorocarbenoid.—Into a flame-dried flask under argon atmosphere was placed 42 g (0.5 mol) of methylene chloride, 92 g (1.0 mol) of norbornadiene, and 100 ml of dried ether. The flask was cooled in an ice bath while 150 ml of 1.7 *N* methyllithium (lithium bromide) (0.25 mol) was added dropwise over 3 hr; the reaction mixture was stirred at room temperature for an additional 1 hr. The reaction was quenched with 100 ml of water and the ether layer was dried ($MgSO_4$), concentrated (rotary evaporator), and distilled at reduced pressure. The distillate, bp 75–80° (10 mm), was treated with excess silver nitrate in aqueous acetone at 60° for 15 min; the organic layer was separated; and the aqueous layer was extracted with ether. The combined organic phases were dried ($MgSO_4$), concentrated (rotary evaporator), and separated by preparative glpc (column D) giving a component which could not be further fractionated but whose nmr spectrum indicated that it was a mixture of **14** (26%) and *exo,anti*-3-chlorotricyclo-[3.2.1.$0^{2,4}$]oct-6-ene (**16**) (74%) [nmr (CCl_4) δ *ca.* 0.8 and 1.1 (m, 2, H_8), 1.38 (m, 2, H_2, H_4), 3.03 (m, 2, H_1, H_5), 3.68 (t, 1, J = 1.5 Hz, H_3), and 6.45 (t, 2, J = 2 Hz, H_6, H_7).

Reductive Dechlorination[16] of *endo,anti*-3-Chlorotricyclo-[3.2.1.$0^{2,4}$]oct-6-ene (14).—Into a dried flask under argon atmosphere was placed 12 ml of dried THF, 2 ml of *tert*-butyl alcohol, 0.5 g of **14**, and 1.0 g of sodium, and the mixture was refluxed for 8 hr. The contents of the flask were allowed to settle and the supernatant liquid was transferred by syringe to a flask containing 10 ml of water. The original reaction flask was rinsed with ether which was similarly transferred to the second flask. The organic layer was separated, dried ($MgSO_4$), and concentrated (rotary evaporator). Preparative glpc of the residue (column C) gave pure *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene (**17**), identical in all respects with the known Diels–Alder adduct of cyclopropene with cyclopentadiene.

General Procedure for Rate Measurements in the Reaction of Tetrachlorocyclopropene (1a) with Cyclopentadiene.—A flask containing 0.710 ml (8.60 mmol) of freshly distilled cyclopentadiene, 0.015 ml of phenylcyclohexane as internal standard, and 3.0 ml of solvent was immersed in a water bath maintained at 25°. Into this solution was rapidly syringed 0.050 ml (0.43 mmol) of tetrachlorocyclopropene (**1a**). Aliquots were removed at selected time intervals through a serum cap and were analyzed by quantitative glpc (column A). Only a small portion (7%) of cyclopentadiene was depleted through dimerization during the course of 1 half-life of the reaction under study. The ratios of the peak areas for product **2a** to standard were determined in each aliquot and the value of $(\mathbf{2a}/\text{standard})_{\text{final}}$ was determined by allowing the reaction to stand at room temperature for several days (corresponding to nearly quantitative conversion of **1a** into **2a**). A plot of log $\{(\mathbf{2a}/\text{standard})_f/[(\mathbf{2a}/\text{standard})_f - (\mathbf{2a}/\text{standard})_t]\}$ *vs.* time yielded a straight line, the slope of which was multiplied by 2.303 and divided by [cyclopentadiene] yielding the second-order rate constants given in Table I. Data from a typical kinetic run are given in Table II. Since analysis of an aliquot taken after only a few seconds showed no product peak, reaction was not occurring either in the injector or on the column. There was no evidence for destruction of the product under these glpc conditions.

TABLE II

KINETIC DATA FROM THE REACTION OF TETRACHLOROCYCLOPROPENE[a] AND CYCLOPENTADIENE[b] IN BENZENE[c] AT 25°

Aliquot	Time, sec	$(\mathbf{2a}/\text{standard})_t$[d]
1	1,922	0.18
2	5,820	0.60
3	7,920	0.72
4	10,440	0.96
5	13,430	1.14
6	*Ca.* 4×10^5	2.90

[a] 0.43 mmol. [b] 8.60 mmol. [c] 3.0 ml containing 0.015 ml of phenylcyclohexane. [d] Ratio of area of product peak to area of standard peak; injector temperature 125°, column temperature 80°.

In both benzene and acetone as solvents, the rate constant was determined under the same conditions except that twice as much cyclopentadiene was employed. The second-order rate constant was unchanged.

Registry No.—**14**, 29119-61-7; **15**, 29119-62-8; **16**, 29119-63-9.

(19) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem.*, **7**, 366 (1957).

(20) (a) S. W. Tobey and R. West, *J. Amer. Chem. Soc.*, **88**, 2478 (1966); (b) S. W. Tobey and R. West, *ibid.*, **88**, 2481 (1966).

The Phenylation of Oxime Anions with Diphenyliodonium Bromide

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The anions of benzophenone oxime (**1**), 4,4-dimethylbenzophenone oxime (**4**), fluorenone oxime (**7**), and *syn*-4-methylbenzophenone oxime (**10**) were phenylated with diphenyl iodonium bromide (DIB). Ambident arylation yielded nitrones and the corresponding *O*-phenyl oximes. The phenylation of the *syn*-4-methylbenzophenone oxime anion yielded the isomerically pure nitrone **12a** and an *O*-phenyl derivative believed to be *syn*-*O*-phenyl 4-methylbenzophenone oxime (**11**). In one arylation this *O*-phenyl oxime was accompanied by an isomeric mixture of *N*,α-diphenyl-α-*p*-tolylnitrones (**12a** and **12b**). Evidence is presented which suggests that equilibration of initial nitrone **12a** of retained geometrical configuration may be effected by unreacted oxime anion. Lower limits of the thermal configurational stabilities of **11** and the two phenylated products of **4** were determined from their nmr spectra at elevated temperature.

Studies of the thermal rearrangement of α,α-diaryl-*N*-benzhydrylnitrones to *O*-benzhydryl diarylketoximes have been reported.[3] While conducting an investigation into the geometric course of this type of rearrangement, it became desirable to prepare model nitrones which might be useful in making geometric assignments to requisite unsymmetrical nitrones. It was also hoped that these model nitrones obtained from the arylation of oxime anions could be used to evaluate the configurational stability of nitrones (at temperatures between 130 and 160°) which are unlikely to isomerize by a dissociation (to an iminoxy and counter-radical pair)–recombination mechanism. The first objective was realized, but the second (because of the thermal instability of the *N*-phenylnitrones) was not.

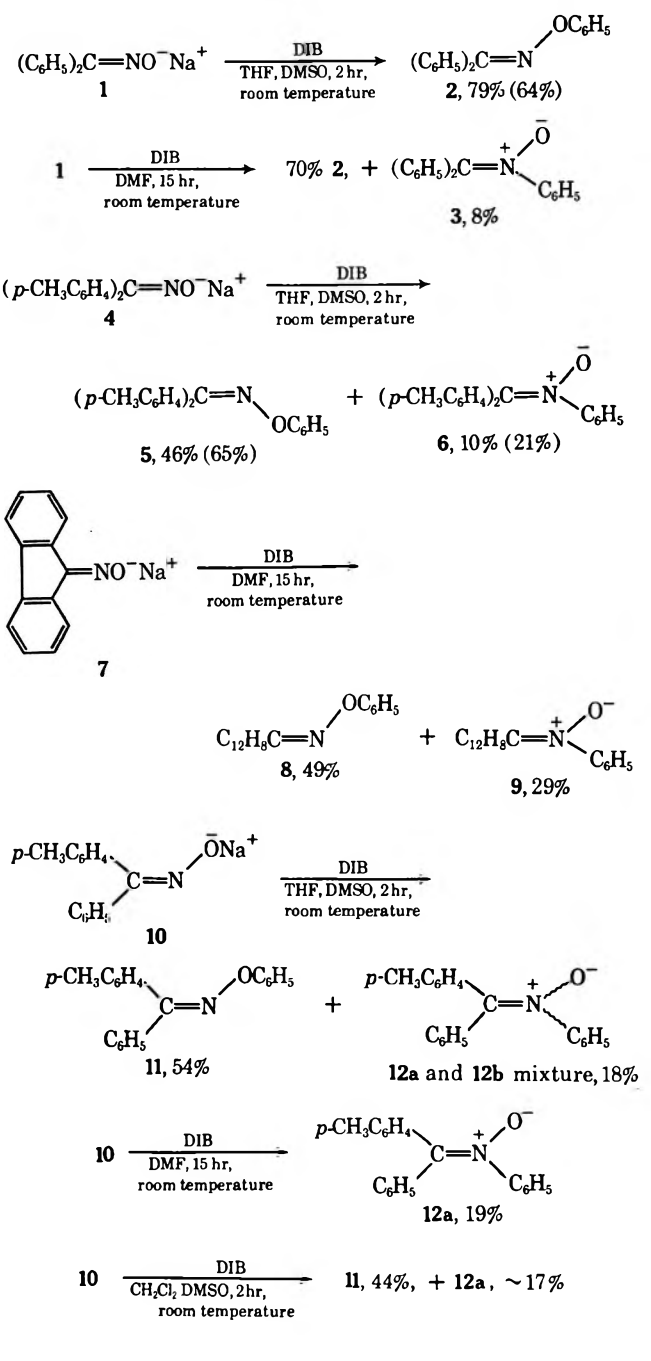
The preparation of *O*-aryl oximes by nucleophilic substitution on haloaromatics bearing strong electron-attracting groups have been reported by several groups.[4] Several examples of the synthesis of *O*-phenyl oximes using *O*-phenylhydroxylamine and carbonyl derivatives have also been described.[5] At the outset of this study no direct phenylation of oxime anions had been reported.[6] However, in view of the success in arylating benzoate, methoxide, and phenoxide anions with diphenyliodonium salts,[7] the potential for arylating oxime anions with such reagents appeared promising. The results discussed below demonstrate that phenylation of oxime anions with diphenyliodonium salts provides a good general route to *N*-phenylnitrones and *O*-phenyl oximes.

Results

Syntheses.—The anions of benzophenone oxime (**1**), 4,4-dimethylbenzophenone oxime (**4**), fluorenone oxime (**7**), and *syn*-4-methylbenzophenone oxime (**10**) were phenylated with diphenyliodonium bromide. The conditions employed and the products obtained are summarized in Scheme I. No extensive survey of reaction conditions designed to maximize yields was made.

Structural Characterization of Products.—The products were characterized by their elemental analyses,

SCHEME I



(1) Author to whom correspondence should be directed.

(2) NSF College Teacher Research Participant, summer 1968.

(3) (a) J. S. Vincent and E. J. Grubbs, *J. Amer. Chem. Soc.*, **91**, 2022 (1969); (b) E. J. Grubbs, J. A. Villarreal, J. D. McCullough, Jr., and J. S. Vincent, *ibid.*, **89**, 2234 (1967); (c) E. J. Grubbs, J. D. McCullough, Jr., B. H. Weber, and J. R. Maley, *J. Org. Chem.*, **31**, 1098 (1966).

(4) See for example (a) E. A. Titov, *Zh. Org. Khim.*, **4**, 882 (1968); (b) A. Mooradian and P. E. Dupont, *J. Heterocycl. Chem.*, **4**, 441 (1967); (e) A. Mooradian and P. E. Dupont, *Tetrahedron Lett.*, 2867 (1967).

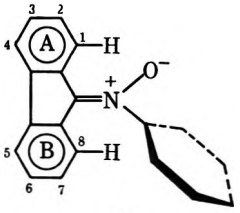
(5) (a) J. H. Cooley, B. N. Misra, J. R. Throckmorton, and W. D. Bills, *J. Med. Chem.*, **11**, 196 (1968); (b) J. S. Nicholson and D. A. Peak, *Chem. Ind. (London)*, 1244 (1962).

(6) During the preparation of this manuscript it came to our attention that an investigation similar to the present one has been conducted by Dr. D. D. Doptoglon under the direction of Professor F. M. Beringer [*Diss. Abstr. B*, **30**, 2082 (1969); *Chem. Abstr.*, **73**, 34978x (1970)].

(7) F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Amer. Chem. Soc.*, **75**, 2708 (1953).

mass spectra, nmr, and, in some cases, ultraviolet spectra. The ultraviolet spectra are particularly useful in distinguishing between the nitrones and *O*-phenyl oximes. With the exception of **9** the nitrones exhibit long wavelength maxima in the region 310–316 mμ.[8] The corresponding *O*-phenyl derivatives **2**, **5**, and **11** show maxima below 300 mμ. The nitrone **9** derived from fluorenone exhibits its longest wavelength absorption at 351 mμ while that of the *O*-phenyl derivative appears at 324 mμ. The mass spectra of the nitrones examined in the present study show the characteristic loss of oxygen from the parent ions. This behavior has been previously observed with a variety of nitrones.[9] By contrast, the spectra of the *O*-phenyl derivatives are characterized by a dominating loss of the phenoxyl group among the various fragmentations.

The nmr spectrum of **9** is particularly interesting. Of the 13 aromatic protons, one appears as a low-field



9

multiplet centered at about 8.9 ppm and one absorbs at unusually high field, appearing as a multiplet centered at approximately 5.9 ppm. The "low-field proton" has been identified as H-1 in accord with the interpretation of the nmr spectra of α,*N*-diphenylnitrones.[10,11] The "high-field proton" absorption can reasonably be assigned to H-8. Interactions between the phenyl group and ring B will force the former into a conformation nearly perpendicular to the rest of the molecule. This places H-8 in the face of this benzene ring accounting for the observed shielding.

Stereochemistry of the Arylation Reaction.—As shown in Scheme I, the phenylation of sodium *syn*-*p*-methylbenzophenone oximate (**10**) under several different conditions led to O- and N-arylation in a ratio of about 3 to 1.[12] Stereospecific arylations were observed in all cases except in the formation of the nitrone in tetrahydrofuran. The stereochemistry of the products was assigned on the following basis. The stereochemistry of the starting oxime has been established by ultraviolet spectral analyses and Beckmann rearrangement.[13] The geometrical assignments of the two 4-methylbenzophenone oximes are also consistent with those arrived at by a comparison of the C–H bending vibrations for para-disubstituted benzenes (in the 830-cm^{-1} region).[14] In both phenylations of **10** from which the *O*-phenyl derivative was isolated (and in reasonably high yield), this compound proved to be isomerically pure. This was suggested by its narrow melting point range but unequivocally demonstrated by the appearance of only one sharp methyl-proton singlet in the nmr.[15] In the two reactions where a geometrically pure nitrone was isolated (in one case accompanying **11**), the nitrone proved to have the same configuration as the starting oxime (see below). Consequently, it is virtually certain that **11** also possesses the "retained" configuration as shown. The configuration of the geometrically pure nitrone **12a** can be assigned on the following basis. Koyano and Suzuki[10] have shown that the ortho protons on the α-phenyl group cis to the oxygen in a series of α,*N*-diarylnitrones absorb at lower field than the remaining aromatic protons. When the α-phenyl group is unsubstituted, this low field absorption is a complex multiplet. However, in every case in which this ring was substituted in the para position (eight examples were provided), these ortho protons gave rise to a doublet.[17] This must be half of an AA′BB′ spectrum with coupling to meta protons which are obscured in the remaining complex aromatic proton absorption at higher field. Consequently, the geometrically pure nitrone **12a** obtained from **10**, which exhibits the two-proton, low-field doublet, possesses the configuration shown.[18]

Variable Temperature Nmr Examination of 5, 6, and 11.—The thermal stabilities of the N- and O-phenylated oximes are much lower than their *N*- and *O*-alkyl analogs. They darken rapidly and decompose to a mixture of unidentified products when heated above their melting points. In solution decomposition occurs rapidly above 100°. Nonetheless, it appeared useful to evaluate at least qualitatively the lower limits of configurational stability of these compounds by nmr.

The proton spectra of *N*-phenyl-α,α-di-*p*-tolylnitrone (**6**) in chlorobenzene were determined at 20° intervals between room temperature and 140°. No coalescing (or peak broadening) was observed in the two methyl singlets.

Similar scans of the pmr spectra of *O*-phenyl-4,4′-dimethylbenzophenone oxime (**5**) in dimethyl malonate were conducted over a range of temperatures up to 145°. Again no coalescing (or peak broadening) of the two methyl singlets was detected. The nmr spectra of *syn*-*O*-phenyl-4-methylbenzophenone oxime (**11**) in dimethyl malonate were examined in the same

(8) See T. Kubota, M. Yamakawa, and Y. Mori, *Bull. Chem. Soc. Jap.*, **36**, 1552 (1963), for a tabulation and discussion of the ultraviolet spectra of nitrones.

(9) See M. Masui and C. Yijima, *Chem. Pharm. Bull.*, **17**, 1517 (1969), and references therein.

(10) K. Koyano and H. Suzuki, *Bull. Soc. Chem. Jap.*, **42**, 3306 (1969).

(11) All of the nitrones we have examined including the *N*-phenylnitrones reported in this study show two protons (or in the case of **9**, one proton) at low field which are undoubtedly the ortho protons of the α-phenyl cis to the nitrone oxygen.

(12) For the arylation conducted in DMF, the oxime anion was generated from the oxime by use of sodium hydride in mineral oil. Difficulty was encountered during chromatographic attempts to separate **11**, iodobenzene, and residual mineral oil.

(13) R. F. Rekker and J. U. Veenland, *Recl. Trav. Chim. Pays-Bas*, **78**, 739 (1959).

(14) Unpublished observations by E. J. Grubbs and T. S. Dobashi. See D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Amer. Chem. Soc.*, **88**, 2775 (1966), for other geometric correlations using this method.

(15) Note that in the nmr spectra of each of the two phenylated products derived from 4,4-dimethylbenzophenone oxime, two well-resolved methyl singlets are observed. Although the geometric isomer of **11** has not yet been isolated in pure form, the two *O*-benzhydryl isomers have.[16] And, as anticipated, the chemical shift difference between the methyl singlets in these two isomers is almost identical with the difference in chemical shift between the two singlets in *O*-benzhydryl 4,4-dimethylbenzophenone oxime.[16]

(16) Unpublished data of E. J. Grubbs and T. S. Dobashi.

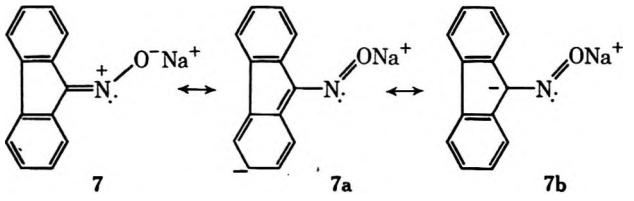
(17) We have observed similar characteristics in the nmr spectra of *N*-benzhydryl-α,α-diphenylnitrone,[3e] *N*-*p*-methylbenzhydryl-α,α-diphenylnitrone,[3e] α,α-di-*p*-tolyl-*N*-benzhydrylnitrone,[3e] α,α-di-*p*-chlorophenyl-*N*-benzhydrylnitrone, and α,α-diphenyl-*N*-methylnitrone. Specifically for those nitrones in which the α-phenyl rings are unsubstituted, a low-field complex multiplet is observed which corresponds to two protons. In the two nitrones para substituted in the α-phenyl rings, this low-field absorption is a doublet.

(18) Mixtures of the two nitrone isomers **12a** and **12b** show the same doublet superimposed upon a complex multiplet.

way up to 115°. No evidence for broadening of the methyl singlet nor for the appearance of a second methyl singlet (which would be characteristic for the anti isomer) was found.

Discussion

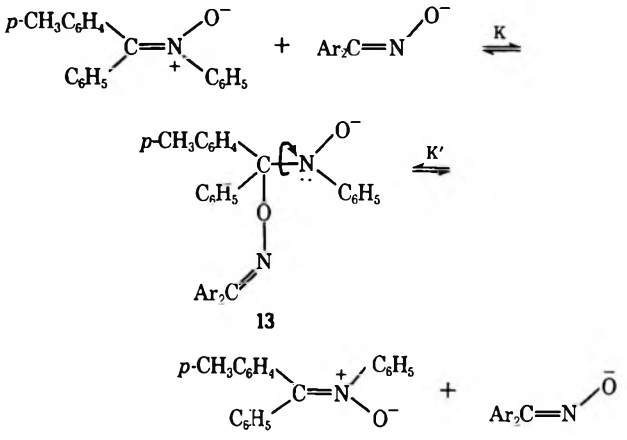
The arylation procedure described has been shown to be an effective route to *N*-arylnitrones and *O*-aryl oximes. The O–N phenylation ratios as determined from yields of isolated products range from about 9:1 for the benzophenone oxime anion to 1.7:1 for the fluorenone oxime anion. It is somewhat surprising that the O–N phenylation ratio is smaller for fluorenone oxime anion than for the benzophenone oxime anion. The aromatic ring (ring B) anti to the oxygen in fluorenone oximate cannot rotate to a conformation perpendicular to the C=N—O plane as is possible with benzophenone oximate. Consequently, one might have anticipated that increased nonbonded interactions between this ring (or specifically H-8) and the phenylating agent in the transition state would lead to a higher O–N phenylation ratio.[19] However, the same conformational restriction in the fluorenone oximate along with ring fusions could lead to a diminution in nucleophilicity at oxygen by greater electron delocalization as suggested by structures **7a**, **7b**, etc. Certainly one might expect the cyclopentadienide-type structures to be



7 **7a** **7b**

significant contributors to the anionic hybrid. The degree and nature of aggregation of **1** and **7** in the reaction solvent system may also play an important role in determining the O–N phenylation ratios for **1** and **7**.[22] This, however, has not yet been demonstrated.

The phenylations proceed with retention of configuration of the parent oxime. In the one reaction which led to a mixture of geometrically isomeric nitrones, equilibration of initially formed geometrically pure nitrone appears likely. Certainly, prior geometric equilibration of the oxime anion did not occur since the accompanying *O*-phenyl derivative isolated in high yield was isomerically pure. The nitrone **12a** is configurationally stable under the work-up conditions including chromatography. However, in the work-up procedure for the phenylation leading to a mixture of **12a** and **12b**, chromatography exhausted the particular lot sample of silica gel. A control experiment with silica gel from a different bottle indicated no geometric isomerization of **12a** on the column. This does not exclude the possibility that the geometric equilibration of **12a** was caused by some contaminant in the original silica gel. Nonetheless, it seemed a reasonable possibility that the isomerization of geometrically pure nitrone might be explained by equilibria involving the nitrones, oximate, and the adduct **13**. Nitrones are



13

known to undergo attack at the α carbon by nucleophiles such as cyanide ion, Grignard reagents, and other carbanions.[23] With this in mind, a sample of pure nitrone **12a** in methylene chloride was treated with approximately 0.5 equiv of sodium benzophenone oximate.[24] Even without the benefit of complete solution, the anion effected equilibration of the nitrone. After being allowed to stand at room temperature for 26 hr, a mixture of 88% **12a** and 12% **12b** was isolated. Only 58% of the nitrone was recovered by efficient chromatographic techniques. This may suggest that the equilibrium constants K and K' may not be insignificant and/or that nitrone may be lost through the formation and possible further reactions of intermediates such as **13**.

An attempt was made to approximate the conditions for the phenylation of **10** [which led to a mixture of **12a** and **12b** (see Scheme I)] as this reaction neared completion. The object was to determine whether under these conditions an excess of oxime anion could geometrically equilibrate either **11** or **12a**. Sodium benzophenone oximate (**1**) was again substituted for **10** to facilitate nmr analyses. An excess of **1** along with appropriate quantities of sodium bromide, iodobenzene, **11**, and **12a** were stirred for 2 hr at room temperature in THF containing DMSO. A work-up and separation procedure not involving water led to the reisolation of approximately 95% of unchanged **11**. However, the nitrone was partially equilibrated (85% **12a** and 15% **12b**) and only 64% was recovered. Clearly, additional experiments would be necessary to unequivocally identify the agent responsible for the nitrone equilibration in the original phenylation of **10** in THF–DMSO. Nonetheless, these observations may well suggest precautions to those contemplating the synthesis of nitrones by geometrically selective alkylation or arylation of oxime anions. Certainly the presence

(19) Kornblum and Seltzer have demonstrated the importance of steric hindrance in ambident alkylations of potassium 2,6-di-*tert*-butyl phenoxide.[20] Smith and Robertson observed a much higher N–O alkylation ratio for sodium benzophenone oximate with methyl bromide than with benzyl bromide and suggested that steric hindrance in the case of benzyl bromide might have increased attack at the less hindered oxygen.[21] Nonetheless, the mechanism of the arylation of oxime anions by diaryliodonium salts is probably quite different than that for alkylations. It is possible that an intramolecular arylation proceeding from an oxime anion–diphenyliodonium ion complex may be less sensitive to steric factors.

(20) N. Kornblum and R. Seltzer, *J. Amer. Chem. Soc.*, **83**, 3668 (1961).

(21) P. A. S. Smith and J. E. Robertson, *ibid.*, **84**, 1197 (1962).

(22) See S. G. Smith and D. V. Milligan [*ibid.*, **90**, 2393 (1968)] for a demonstration of the effect of ion pairing of **7** on the site of alkylation by methyl iodide.

(23) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964).

(24) The anion derived from benzophenone oxime rather than from one of the 4-methylbnzophenone oximes was used so that equilibration could be more easily followed by nmr without complication from the methyl singlets of the oximes.

of excess base even in the form of the oxime anion should be avoided.

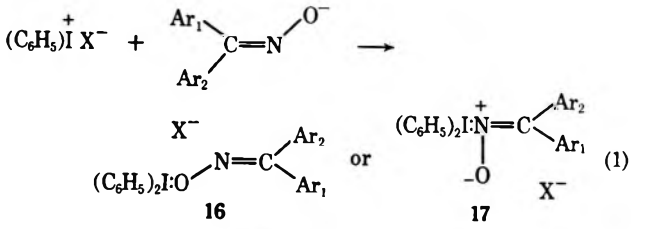
One further consequence of the observation of geometric specificity in the arylations of oxime anions deserves comment. Ptitsyna, Lyatiev, and Reutov have recently investigated the mechanism of the reaction of diphenyliodonium salts with amines.[25] Their results suggest that the first step is the formation of a complex such as **14**. With aliphatic amines they propose a dissociation of this complex to the diphenyliodine radical and a radical cation **15** which forms the salt of the amine by hydrogen atom abstraction.

$$(C_6H_5)_2\overset{+}{I}\,\overset{-}{X} + :NR_3 \longrightarrow \underset{\mathbf{14}}{(C_6H_5)_2I{:}\overset{+}{N}R_3\,X^-}$$

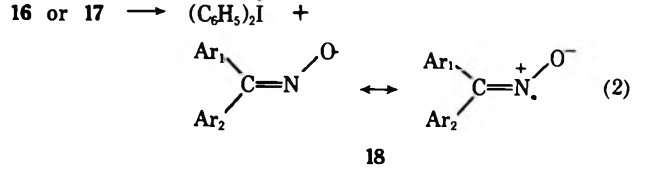
$$14 \longrightarrow (C_6H_5)_2I\cdot + \underset{\mathbf{15}}{\cdot\overset{+}{N}R_3\,X^-}$$

$$15 + SH \longrightarrow H\overset{+}{N}R_3\,X^-$$

If oxime anions form similar complexes in the presence of diaryliodonium salts, the least that can be said is that dissociation to free radicals probably occurs slowly, if at all, and the principal route to product formation apparently does not follow step 2. A growing body of evidence indicates that unsymmetrical



(1)



(2)

iminoxy radicals equilibrate extremely rapidly forming a mixture of two geometric isomers.[26-29] Admittedly,

the relationship between the configurational properties of iminoxy radicals and their proximity to other radicals or the degree to which they exist in solvent "cages" has not been determined. Nonetheless, since geometric specificity was observed in the arylation of **10**, free iminoxy radicals are unlikely precursors.

Because of the thermal instability of *N*-phenylnitrones and *O*-phenyl ketoximes, only limited information regarding their configurational stabilities was obtained. However, on the basis of the variable-temperature nmr study, it can be safely concluded that configurational isomerization about the carbon–nitrogen double bonds in these oxime derivatives is slow by the nmr time scale.

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(27) (a) J. R. Thomas, *J. Amer. Chem. Soc.*, **86**, 1446 (1964); (b) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc., B*, **86** (1966); (c) M. Bethoux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim., Fr.*, 1985 (1964).

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Experimental Section[30]

The Phenylation of Sodium Benzophenone Oximate (1). A. In Tetrahydrofuran Containing DMSO.—The sodium salt of benzophenone oxime was prepared from 5.00 g (0.0254 mol) of benzophenone oxime and 1.00 g (0.043 g-atom) of sodium in 40 ml of tetrahydrofuran. After hydrogen evolution had ceased, the excess sodium was removed. Dimethyl sulfoxide (15 ml) was added. Diphenyliodonium bromide (DIB)[7] (9.00 g, 0.0250 mol) was then added in portions over a 15-min period. An additional 15 ml of THF was added and the mixture stirred under nitrogen for 2 hr at room temperature. The mixture was poured into 200 ml of cold water and extracted with three 100-ml portions of methylene chloride. The extract was washed with water, dried, and concentrated to a yellow oil containing a white solid. Trituration of this crude product with hexane and filtration served to remove 0.95 g of unreacted DIB, mp 215–217° dec. The hexane filtrate was concentrated under reduced pressure (to remove solvent and iodobenzene) and chromatographed on 80 g of silicic acid. The product was eluted with methylene chloride affording 5.63 g of a pale yellow oil. This was dissolved in 25 ml of a 1:1 ether–hexane solution from which 2 (4.80 g, 79%) was deposited as pale cream-colored crystals, mp 53.0–54.5°. A sample was crystallized again from the same solvent mixture affording white crystals: mp 55.5–56.5°; nmr (CCl_4) 6.9–7.7 (m, aromatic protons); ir (KBr) 1210 cm^{-1} (CO); uv (C_2H_5OH) λ_{max} (ϵ) 222 (22,700), 270 (11,500), 289 mμ (11,500); mass spectrum (15 eV) *m/e* 273 (10) (parent ion), 180 (100) (P − C_6H_5O).

Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13. Found: C, 83.78; H, 5.61; N, 5.00.

A similar phenylation of benzophenone oxime in THF using sodium hydride to generate the oxime anion afforded **2**, mp 54.5–55.5°, in 64% yield.

B. In Dimethylformamide.—The oxime (45.0 g, 0.228 mol) in 250 ml of dimethylformamide was treated with 10.1 g (0.226 mol) of sodium hydride (52% in mineral oil). After evolution of hydrogen had ceased, 83.0 g (0.230 mol) of DIB was added. The reaction mixture was stirred overnight at room temperature, poured into water, and extracted with ether. Some of the crude nitrone **3** (4.08 g, mp 197–211°) crystallized from the mixed organic phase. Concentration of the resulting organic filtrate afforded an additional precipitate which when crystallized from methanol yielded 3.93 g of impure **3**, mp 208–216°. All remaining residual oils were combined and chromatographed over a mixture of 90 g of silicic acid and 10 g of Celite. Elution with hexane and crystallization from methanol yielded 42.1 g (70% based on unrecovered oxime) of **2**, mp 50–52°. Further purification of this sample by chromatography and crystallization from pentane afforded 29.5 g (49%) of **2** as white crystals, mp 53–54°. Elution with benzene afforded 1.83 g of unreacted oxime (mp 140.5–142°). Elution with 10–50% ether in methylene chloride gave 0.93 g of the impure nitrone, mp 208–216°. This was combined with the 8.01 g of impure **3** isolated earlier and recrystallized from aqueous ethanol to give 6.92 g (11%) of **3**, mp 218.5–224°. A portion of this sample (4.65) was recrystallized again from aqueous ethanol affording 3.12 g (8% corrected according to sample size used in final crystallization) of **3**: mp 222.5–224° [lit.[31] mp 223–225°; uv (C_2H_5OH) λ_{max} (log ϵ) 310 (4.0), 231 mμ (4.2)]; nmr ($CDCl_3$) 7.8–8.2 (m, 2, aromatic), 6.9–7.5 (m, 13, aromatic); uv (C_2H_5OH) λ_{max} 311 (10,900), 232 mμ (15,300); mass spectrum (80 eV) *m/e* 273 (100) (parent ion), 257 (74) (P − oxygen).

(30) All melting points are corrected. The infrared spectra were determined on a Perkin-Elmer Model 621 grating spectrophotometer. Proton magnetic resonance spectra were obtained using a Varian Model A-60 spectrometer. The chemical shifts are relative to tetramethylsilane used as an internal reference. Mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E spectrometer. Elemental analyses were performed by M-H-W Laboratories (Garden City, Mich.).

(31) A. W. Johnson, *J. Org. Chem.*, **28**, 252 (1963).

Phenylation of Sodium 4,4′-Dimethylbenzophenone Oximate (4).—A 10.0-g (0.0444 mol) sample of the oxime was converted to its sodium salt (with sodium) in 75 ml of THF. Dimethyl sulfoxide (10 ml) was added followed by the addition of 14.4 g (0.0400 mol) of DIB over a 15-min period. The mixture was stirred for 2 hr at room temperature and then worked up as before. Addition of 40 ml of pentane to the oily reaction product resulted in the crystallization of 1.75 g (15%) of crude *N*-phenyl-α,α-di-*p*-tolylnitrone (6), mp 162–165°. Recrystallization of the nitrone from 125 ml of ether afforded 1.16 g (10%) of 6 as colorless crystals: mp 166.5–167.5°; nmr (CCl_4) 2.27, 2.38 (2 s, 6, CH_3), 6.9–8.05 (m, 13, aromatic); uv (C_2H_5OH) λ_{max} 316 (11,800), 253 (15,400), 236 mμ (15,700); mass spectrum (80 eV) *m/e* 301 (100) (parent ion), 285 (48) (P − oxygen).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69, H, 6.35; N, 4.65. Found: C, 83.60, 83.83; H, 6.48, 6.26; N, 4.60, 4.69.

The pentane filtrate from which the nitrone first crystallized was cooled further, whereupon 7.87 g (67%) of impure *O*-phenyl 4,4′-dimethylbenzophenone oxime (5) deposited as pale yellow crystals, mp 65–69°. Two recrystallizations of the crude *O*-phenyl oxime from 1:4 ether–hexane gave 4.80 g of 5, mp 71.5–74.0°, which was still contaminated with nitrone 6. Chromatography of this material (plus the crude product obtained by concentrating the pentane filtrate above) over 100 g of 60–200 mesh silica gel led to the isolation of 5.43 g (46%) of colorless 5: mp 74.5–75.5° (along with an additional 0.30 g of nitrone 6, mp 165–167°); nmr (CCl_4) 2.32, 2.37 (2 s, 6, CH_3), 6.65–7.90 (m, 13, aromatic); uv (C_2H_5OH) λ_{max} 291 (12,930), 269 (13,560), 265 (13,250), 242 mμ (19,500); mass spectrum (15 eV) *m/e* 301 (1) (parent ion), 208 (100) (P − C_6H_5O).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.52, 83.81; H, 6.41, 6.33; N, 4.65, 4.59.

The filtrates obtained from the crystallizations which had afforded 4.80 g of 5 above were concentrated. The concentrate was chromatographed as previously described to give an additional 1.38 g of 5, mp 74.0–75.0°.

A second phenylation of 10.0 g of sodium 4,4′-dimethylbenzophenone oximate under the same conditions afforded 65% of the *O*-phenyl derivative 5 and 21% of the nitrone 6.

Phenylation of Sodium Fluorenone Oximate (7).—A cooled (0°) solution of 9.75 g (0.0500 mol) of fluorenone oxime in 125 ml of dimethylformamide (distilled from calcium hydride) was treated with 2.4 g (0.050 mol) of sodium hydride (52% in mineral oil). After the evolution of hydrogen had ceased, 18.05 g (0.0500 mol) of DIB was added. The mixture was stirred overnight at room temperature and poured into 500 ml of water. Ether (125 ml) was then added. An insoluble crystalline material was collected and dried to give 3.81 g of yellow needles, mp 185–191°. The ether layer above was separated and the aqueous phase extracted twice with 125-ml portions of ether. The combined ether extract was dried and concentrated, whereupon an additional 0.63 g (mp 190–191.5°) of the nitrone 9 was deposited. The combined sample of crude nitrone was recrystallized from aqueous ethanol to give 3.98 g (29%) of *N*-phenyl-α,α-[2,2′-diphenylene]nitrone (9) as yellow needles: mp 193–194.5° [lit.[31] mp 194–196°; uv (C_2H_5OH) λ_{max} (log ε) 351 (4.3), 260 (4.4), 236 mμ (4.5)]; nmr ($CDCl_3$) 5.8–6.0 (m, 1, aromatic), 6.7–7.8 (m, 11, aromatic), 8.8–9.05 (m, 1, aromatic); uv (C_2H_5OH) λ_{max} 351 (16,300), 340 sh (13,800), 296 (6250), 267 sh (19,800), 261 (20,800), 242 (35,800), 236 mμ (37,400); mass spectrum (80 eV) *m/e* 271 (100) (parent ion), 255 (65) (P − O).

Several unsuccessful attempts were made to crystallize the *O*-phenyl fluorenone oxime 8 from the residue obtained from concentrating the filtrates retained after crystallizing the nitrone. This residue was then subjected to a combination of chromatography over Florisil [and alternately SilicAR CC-7 (Mallinckrodt silicic acid)] and crystallization from methanol affording 0.62 g of 9, mp 192.5–194° (second crop, 0.16 g, mp 182–188°), and 6.61 g (49%) of 8 as pale yellow crystals, mp 93.5–95.5°. A 3.41-g sample of this *O*-phenyl oxime was recrystallized three times from methanol to give 2.07 g of pale yellow needles: mp 95–96°; nmr (CCl_4) 6.8–7.95 (m, 12, aromatic), 8.23–8.47 (m, 1, aromatic); uv (C_2H_5OH) λ_{max} 324 (13,600), 276 (7,720), 256 (49,200), 248 mμ (41,100); mass spectrum (15 eV) *m/e* 271 (100) (parent ion), 178 (95) (P − C_6H_5O).

Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 84.15; H, 4.71; N, 4.92.

Phenylation of Sodium *syn*-4-Methylbenzophenone Oximate (10). A. In Tetrahydrofuran Containing DMSO.—The reaction was conducted using essentially the same conditions as described for the phenylation of the 5-g sample of benzophenone oxime (sodium used to generate anion). The oxime anion (generated from 2.11 g, 0.010 mol of oxime) was allowed to react with 3.1 g (0.0090 mol) of DIB in boiling THF (20 ml) containing 3 ml of DMSO for 2 hr. Following a similar work-up procedure, 3.05 g of crude product was chromatographed on 200 g of silica gel. Elution with a 1:1 mixture of methylene chloride and pentane afforded 1.97 g of *O*-phenyl-*syn*-4-methylbenzophenone oxime (11), mp 72–78°. This was recrystallized from 10 ml of 10% ether in hexane to give 1.55 g (54%) of 11 as colorless crystals, mp 77.5–79.5°. Two additional crystallizations afforded analytically pure 11: mp 78.5–80.0°; nmr (CCl_4) 2.40 (s, 3, CH_3), 6.5–7.8 (m, 14, aromatic); uv (C_2H_5OH) λ_{max} 222 (22,500), 235 sh (19,100), 264 sh (11,200), 269 (11,700), 288 mμ (11,600); mass spectrum (15 eV) *m/e* 287 (8) (parent ion), 194 (100) (P − C_6H_5O).

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.97; N, 4.88. Found: C, 83.56, 83.49; H, 5.91, 5.97; N, 4.98, 4.95.

Elution with 1:1 ether–methylene chloride afforded 0.52 g (18%) of a mixture of the geometrically isomeric *N*,α-diphenyl-α-*p*-tolylnitrones (12a and 12b): mp 180–184°; nmr (CD_3COCD_3) 2.26, 2.37 (2 s, 3, CH_3), 6.8–8.2 (m, 14, aromatic); uv (C_2H_5OH) λ_{max} 233 (15,200), 248 (14,600), 312 mμ (11,700).

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.97; N, 4.88. Found: C, 83.70; H, 6.01; N, 4.90.

A control experiment with pure 12a but using a different lot sample of silica gel showed no geometric equilibration of the nitrone employing the elution procedure described for the isolation of the mixture of 12a and 12b above.

B. In Dimethylformamide.—The oxime anion 10 was generated from 11.62 g (0.055 mol) of the oxime and 2.70 g (0.055 mol) of 52% sodium hydride (in mineral oil) in 100 ml of dimethylformamide. The resulting mixture was treated with 19.9 g (0.055 mol) of DIB. The reaction mixture was stirred overnight at room temperature, poured into water, and extracted with ether. The dried ether extract was concentrated under vacuum. The residue was dissolved in hexane from which 3.16 g of 12a deposited in three crops, mp 183–186°. This was recrystallized from aqueous ethanol to give 2.95 g (19%) of white crystalline 12a, mp 186–191.5°. An analytical sample was obtained by recrystallizing a small sample twice from a 40:60 aqueous ethanol mixture, mp 189–192°.

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.97; N, 4.88. Found: C, 83.65; H, 6.14; N, 4.83.

The nmr spectrum ($CDCl_3$) of 12a showed the following absorptions: 2.37 (s, 3, CH_3), 6.9–7.35 (m, 12, aromatic), 7.93 (d, 2, aromatic); mass spectrum (15 eV) *m/e* 287 (100) (parent ion), 271 (78) (P − oxygen).

C. In Methylene Chloride Containing DMSO.—The sodium salt 10 was prepared in 20 ml of methylene chloride by allowing 1.05 g (0.0050 mol) of the oxime to react with 0.121 g (0.0052 g-atom) of sodium. DIB (1.80 g, 0.0050 mol) was then added, followed by 1.5 ml of DMSO. A vigorous reaction appeared to take place immediately. The reaction mixture was allowed to stand for 2 hr. Sodium bromide was separated by filtration and the filtrate concentrated under reduced pressure. The residue was chromatographed over 70 g of Florisil. Elution with hexene afforded 0.624 (44%) of 11 as white crystals, mp 78–80°. One recrystallization from aqueous methanol (affording 0.414 g) raised the melting point to 79.5–81°. Elution with 50% ether in benzene yielded 0.247 g (17%) of the nitrone 12a, mp 186–190°. This was recrystallized from aqueous methanol and then aqueous ethanol affording 0.094 g of pure 12a, mp 188–191.5°. The nmr spectra for 11 and 12a were identical with those reported above. Each showed only one methyl singlet attesting to their isomeric purity.

Geometric Equilibration of *syn*-α,*N*-Diphenyl-α-(*p*-tolyl)nitrone (12a) by Sodium Benzophenone Oximate. A. In Dichloromethane.—A suspension of sodium benzophenone oximate in 25 ml of methylene dichloride was prepared from 0.940 g (4.76 mmol) of the oxime and an excess sodium. To this suspension (freed of remaining sodium) was added 0.274 g (0.965 mmol) of the nitrone 12a. The mixture was allowed to stand at room temperature. Aliquots were removed periodically in order to monitor the nitrone equilibration by nmr. This was done by following the steady increase of the methyl singlet at 2.26 ppm for the "anti" nitrone 12b. The methyl singlet corresponding to the "syn" nitrone appears at 2.37 ppm. After 26 hr the mixture was filtered to remove most of the sodium benzo-

phenone oximate. The filtrate was concentrated. The residue was then chromatographed over 10 g of Florisil. Elution with 20% ether in methylene chloride afforded 0.160 g (58% recovery) of a mixture of the isomeric nitrones **12a** and **12b**, mp 175–187°. The ratio of integrated areas of the methyl singlets corresponding to **12a** and **12b** indicated the presence of 88% **12a** and 12% **12b**. An elemental analysis (C, H, and N) of this mixture was in excellent agreement with the calculated values.

B. Tetrahydrofuran Containing DMSO.—Sodium benzophenone oximate (0.50 mmol) was liberated from 0.099 g (0.50 mmol) of the oxime by 1 equiv of sodium in 25 ml of dry, freshly distilled THF. Anhydrous sodium bromide (0.182 g, 1.77 mmol) and 0.360 g (1.77 mmol) of iodobenzene were then added. To this mixture was added 0.115 g (0.40 mmol) of **12a** and 0.394 g (1.37 mmol) of the *O*-phenyl isomer **11**. Dimethyl sulfoxide (1 ml) was added and the reaction mixture stirred under dry nitrogen for 2 hr. The mixture was filtered. The THF and most of the DMSO and iodobenzene were removed under reduced pressure. An nmr spectrum of the residue showed methyl singlets characteristic of **11** and **12a** along with a much smaller peak attributable to **12b**. This residue was chromatographed over 25 g of Florisil. Elution with hexene afforded 0.387 g of **11**. The individual fractions containing **11** possessed melting point ranges of 2° or less in the region of 76–79°. The nmr and ir spectra of the combined fractions were essentially identical with those of pure **11**. Only one sharp methyl singlet was observed. Traces of iodobenzene appeared to be the only impurity. Elution with 20% ether in dichloromethane afforded 0.073 g of a mixture of **12a** and **12b**.[32] The nmr spectrum of this mixture was nearly identical with that of the nitrone mixture obtained from the equilibration in dichloromethane. However, in this case integration of the two methyl singlets indicated the mixture to be slightly richer in **12b** (approximately 85% **12a**–15% **12b**).

Configurational Stability of *N*-Phenylnitrones and *O*-Phenyl Oximes. A. *N*-Phenyl-α,α-di-*p*-tolylnitrone (6).—In chlorobenzene, the two methyl singlets are separated by 0.23 ppm at room temperature. The effect of temperature upon these two singlets was studied over the range room temperature to 140°. From 40°, the spectra were determined at 20° intervals. Although at 140° the difference in chemical shifts had decreased very slightly from 0.23 to 0.19 ppm, no other changes were visible. No peak broadening whatever was observed over this temperature range.

B. *O*-Phenyl-4,4′-dimethylbenzophenone Oxime (5).—Three separate samples of **5** were dissolved in dimethyl malonate (DMM). The nmr spectra of the first solution (containing 0.0306 g of **5**) were recorded in 15° increments from room temperature to 115°. The sample was held at each temperature level for 10 min. The sample solution was cooled to room temperature and the spectrum determined again. The spectra were essentially identical at all temperatures. Most of the DMM was removed by distillation under reduced pressure. The residue was chromatographed over 3 g of Florisil. Elution with hexane yielded 0.027 g (88% recovery) of **5**, mp 71.5–72.5°. The nmr and ir spectra of recovered **5** and starting **5** were identical.

The second sample (0.0366 g) of **5** in DMM was heated to 130° in the variable temperature probe. The nmr spectrum was very similar to that of **5** at room temperature. When the probe temperature was raised to 145°, the spectrum had changed radically suggesting decomposition. When the sample was cooled to room temperature, the nmr spectrum remained identical with that obtained at 145°. The DMM was removed under reduced pressure. Chromatographic analysis revealed the presence of at least four different compounds. One, although in impure form (mp 70–74°), has been tentatively identified as 4,4′-dimethylbenzophenone on the basis of its infrared spectrum.

The third sample (0.0325 g in 0.2 ml of DMM) was heated to 130°. The spectrum was quickly determined and the sample returned to room temperature and the spectrum determined again. The spectra at room temperature and at 130° (after approximately 6.5 min at this temperature) were nearly identical. The DMM was removed under reduced pressure and the residue chromatographed as before to give 0.025 g (77% recovery) of **5**, mp 72–73.5°.

C. *syn*-*O*-Phenyl-4-methylbenzophenone Oxime (11).—The nmr spectra of a sample of **5** (0.0317 g, mp 77.5–78.5°) in 0.2 ml of DMM were determined at 15° intervals between room temperature and 115°. The sample was maintained at each temperature level for 10 min prior to obtaining the spectrum. All spectra were identical. No evidence for the appearance of a second methyl singlet nor for broadening was found. The solvent was removed under reduced pressure. The residue was chromatographed as before to give 0.027 g of **11**, mp 75.5–77.5°.

(32) Small additional amounts of **12a** and **12b** were eluted in several intermediate fractions containing a third component which appears to be benzophenone. Consequently the yield of recovered nitrones (64%) may be 5–10% lower than that in the reaction mixture.

Registry No.—**1**, 29127-86-4; **2**, 29127-87-5; **3**, 4504-13-6; **4**, 29127-89-7; **5**, 29127-90-0; **6**, 29127-91-1; **7**, 20474-42-4; **8**, 29127-93-3; **9**, 4535-09-5; **10**, 29119-35-5; **11**, 29119-36-6; **12a**, 29119-37-7; **12b**, 29119-38-8; diphenyliodonium bromide, 1483-73-4.

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Halomethyl Metal Compounds. XLVI. Reaction of Phenyl(bromodichloromethyl)mercury with Heteroatom Cumulenes[1,2]

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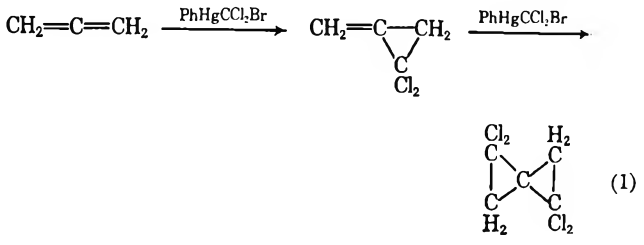
The reactions of phenyl(bromodichloromethyl)mercury with diisopropyl- and dicyclohexylcarbodiimide, phenyl and isopropyl isothiocyanate, phenyl isocyanate, and *trans*-1,2-diisocyanatoethylene, and with carbon disulfide have been studied. The products of the reaction with the carbodiimides are the dichloroimine, $RN{=}CCl_2$, and the isonitrile, $RN{\equiv}C$. With the isothiocyanates the major isolated product is perchlorothiirane, and this compound also is the major product in the reaction with carbon disulfide. *trans*-1,2-Diisocyanatoethylene reacts to give the expected dichlorocyclopropane in 84% yield, but the isocyanate function can react with the mercurial. Thus, reaction of $PhHgCCl_2Br$ with phenyl isocyanate gives *N*-phenyl-*C*-tetrachloroaziridine in 15% yield. These reactions can be generalized in terms of the overall process: $Y{=}C{=}Z + PhHgCCl_2Br \rightarrow PhHgBr + Cl_2C{=}Y + C{\equiv}Z$; $Cl_2C{=}Y + PhHgCCl_2Br \rightarrow PhHgBr + Cl_2C(Y)CCl_2$.

The addition of phenyl(trihalomethyl)mercury-derived dihalocarbenes to olefinic C=C bonds to give *gem*-dihalocyclopropanes[6] is by now a well-known reaction and is finding increasing application in organic synthesis.[7] More recently we have reported successful CX_2 transfer *via* phenyl(trihalomethyl)mercurials to compounds containing the C=N,[8] C=S,[9] and C=O[10] bonds. Among the olefins which were converted to *gem*-dichlorocyclopropanes *via* $PhHgCCl_2Br$ was allene (eq 1).[6] In view of this successful, stepwise CCl_2 transfer to the simplest all-carbon cumulene, it was of interest to examine the reactions of phenyl(bromodichloromethyl)mercury with heteroatom cumulenes of type Y=C=Y and Y=C=Z. Among the systems chosen for study were carbodiimides, carbon disulfide, isothiocyanates, and isocyanates.



(1)

Results

Successful CX_2 transfer to a C=N bond *via* $PhHgCX_3$ reagents to give an aziridine is possible when the nucleophilic character of the nitrogen atom has been significantly decreased.[8] Thus, compounds of type $RN{=}CCl_2$ could be converted to *C*-perchloroaziridines in good yield by reaction with phenyl(bromodichloromethyl)-mercury, but imines of type $RN{=}CHR'$ and $RN{=}CR'_2$ appeared to react with these mercury reagents in other ways to give complex product mixtures. In view of this, one might expect to find that phenyl(bromodichloromethyl)mercury transfers CCl_2 to C=N bonds of carbodiimides. It is known that the nitrogen atoms of carbodiimides have a very low basicity and very little nucleophilic reactivity.[11]

When phenyl(bromodichloromethyl)mercury and diisopropylcarbodiimide were allowed to react in 1:1 molar ratio in benzene at reflux, phenylmercuric bromide precipitation was complete within 20 min. One major and five minor products were present. The major product, formed in 63% yield (based on eq 2), was *N*-isopropyldichloroimine, $Me_2CHN{=}CCl_2$. One of the minor products was isolated in an amount sufficient for spectroscopic characterization as isopropylisonitrile. The other minor products were shown (in an independent experiment) to arise from the complex reaction of phenyl(bromodichloromethyl)mercury with isopropylisonitrile and were not identified.[12] The reaction which occurs between phenyl(bromodichloromethyl)mercury and the carbodiimide thus appears to be that shown in eq 2.

$$Me_2CHN{=}C{=}NCHMe_2 + PhHgCCl_2Br \longrightarrow Me_2CHN{=}CCl_2 + Me_2CHN{\equiv}C + PhHgBr \quad (2)$$

Attempts to increase the isopropylisonitrile yield by increasing the ratio of carbodiimide to $PhHgCCl_2Br$ used to 10 failed. It would appear that the isonitrile is far more reactive toward the mercury reagent than is the carbodiimide. When the $Me_2CHN{=}C{=}NCHMe_2$–$PhHgCCl_2Br$ ratio was decreased to 1:2, the yield of *N*-isopropyldichloroimine was increased to 92%. Phenyl(bromodichloromethyl)mercury reacted in similar fashion with dicyclohexylcarbodiimide to give *N*-cyclohexyldichloroimine as major product.

As we discovered later,[8] *N*-organodichloroimines also react with phenyl(bromodichloromethyl)mercury, giving *N*-organo-*C*-tetrachloroaziridines. The present

(1) Part XLV: D. Seyferth and D. C. Mueller, in press.

(2) Preliminary communication: D. Seyferth and R. Damrauer, *Tetrahedron Lett.*, 189 (1966).

(3) National Institutes of Health Predoctoral Fellow, 1964–1967.

(4) Postdoctoral Research Associate, 1968–1969.

(5) National Institutes of Health Postdoctoral Fellow, 1969–1970.

(6) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J.-H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

(7) Complete listings of new examples of $PhHgCX_3$ reactions can be found in *Organometal. Chem. Rev., Sect. B.*

(8) D. Seyferth and W. Tronich, *J. Organometal. Chem.*, **21**, P3 (1970).

(9) D. Seyferth and W. Tronich, *J. Amer. Chem. Soc.*, **91**, 2138 (1969).

(10) D. Seyferth and W. Tronich, *J. Organometal. Chem.*, **18**, P8 (1969).

(11) (a) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York, N. Y., 1965; (b) I. T. Millar and H. D. Spingall, "Sidgwick's Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1966.

(12) A. Halleux, *Angew. Chem.*, **76**, 889 (1964), has reported that cyclohexylisonitrile reacts with dichlorocarbene (generated by the reaction of potassium alkoxide with chloroform or ethyl trichloroacetate) to give $C_6H_{11}N{=}C(OR)CCl_2H$. This observation, however, may not be relevant to the present case since the reaction of $PhHgCCl_2Br$ with the nucleophilic isonitrile very likely does not proceed *via* a free CCl_2 intermediate.

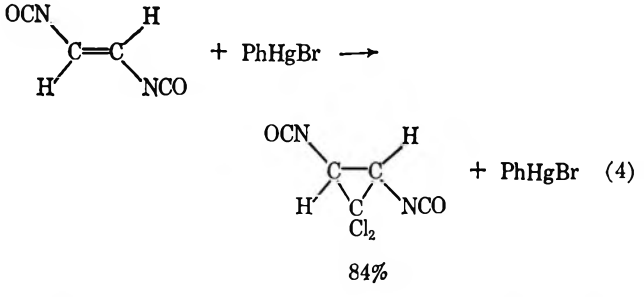
results indicate that the carbodiimides are rather more reactive toward this organomercury reagent than are the RN=CCl_2 products of the $PhHgCCl_2Br$–RN=C=NR reaction.

The reaction of phenyl(bromodichloromethyl)mercury with a slight excess of phenyl isothiocyanate at 70–75° resulted in formation of phenylmercuric bromide and only one major volatile product, identified as perchlorothiirane (59%), which is the product of the reaction of phenyl(bromodichloromethyl)mercury with thiophosgene.[9] The yield of perchlorothiirane could be improved to 74% (based on eq 3) by using a procedure in which the organomercury reagent (2 molar equiv) was added to the phenyl isothiocyanate (1 molar equiv) solution in two portions rather than all at once. Attempts to find PhN=CCl_2 among the products were unsuccessful. The reaction of phenyl(bromodichloromethyl)mercury with isopropyl isothiocyanate also gave perchlorothiirane as the major product. The expected isonitriles were not isolated, and it is assumed that they were almost totally consumed in reaction with the mercurial. The reaction occurring between phenyl(bromodichloromethyl)mercury and isothiocyanates thus would appear to be that shown in eq 3.

$$RN{=}C{=}S + PhHgCCl_2Br \longrightarrow Cl_2C{=}S + RN{\equiv}C + PhHgBr \quad (3)$$

$Cl_2C{=}S$ —($PhHgCCl_2Br$)→ $Cl_2C(S)CCl_2$

Phenyl(bromodichloromethyl)mercury reacts with allyl isocyanate to give 2,2-dichlorocyclopropylcarbinyl isocyanate in 60% yield,[6] and we have found that *trans*-1,2-diisocyanatoethylene is converted to the cyclopropane in high yield by this mercurial (eq 4). Thus,



the NCO function is very much less reactive toward $PhHgCCl_2Br$ than is the olefinic double bond, but the N=C bond of the NCO group does enjoy a small measure of reactivity toward this mercury reagent. When a reaction was carried out at 80° in benzene solution between phenyl(bromodichloromethyl)mercury and a fivefold excess of phenyl isocyanate, one major high-boiling product (9% yield, based on eq 5), 1-phenyl-2,2,3,3-tetrachloroaziridine, was formed. No *N*-phenyldichloroimine was present, within the limits of glc detection. When this reaction was carried out at 90° in the absence of benzene diluent, the yield of the aziridine was raised to 15%. The reactions which appear to be occurring are those shown in eq 5.

The reaction of phenyl(bromodichloromethyl)mercury in twofold excess with carbon disulfide in benzene solution at 70–75° resulted in precipitation of phenylmercuric bromide. Perchlorothiirane was the major volatile product formed, but the yield was low, averaging 25–30% in several reactions. Increasing the mercurial to CS_2 ratio did not serve to raise the perchlorothiirane yield nor did a lower reaction temperature. Equation 6 summarizes the reactions which would appear to be responsible for the formation of perchlorothiirane.

$$PhN{=}C{=}O + PhHgCCl_2Br \longrightarrow PhN{=}CCl_2 + C{\equiv}O + PhHgBr \quad (5)$$

$PhN{=}CCl_2$ —($PhHgCCl_2Br$)→ $Cl_2C(N(Ph))CCl_2$

$$PhHgCCl_2Br + S{=}C{=}S \longrightarrow Cl_2C{=}S + [C{\equiv}S] + PhHgBr \quad (6)$$

$Cl_2C{=}S$ —($PhHgCCl_2Br$)→ $Cl_2C(S)CCl_2$

Discussion

Under the reaction conditions employed, all of the identifiable reactions of phenyl(bromodichloromethyl)mercury with the heteroatom cumulenes which we have investigated appear to take a common course (eq 7).

$$Y{=}C{=}Z + PhHgCCl_2Br \longrightarrow \overset{+}{Y}{=}C{=}Z\ (\overset{-}{C}Cl_2)\ \text{III} \xrightarrow{?} Y{-}C(Cl_2){=}Z\ \text{IV} \quad (7)$$

III, IV → $Cl_2C{=}Y + C{\equiv}Z$

Further reaction of $Cl_2C{=}Y$ with phenyl(bromodichloromethyl)mercury occurs when this product is more reactive toward this mercurial than are Y=C=Z and C≡Z or when the mercurial is used in excess. We know nothing concerning the actual mechanism of these reactions. However, it should be pointed out that in the cases of the carbodiimides, isothiocyanates, isocyanates, and carbon disulfide we are dealing with substrates with available lone electron pairs. As we have shown previously, reactions of tertiary phosphines[13] and tertiary amines[14] with $PhHgCX_3$ compounds appear to proceed *via* direct attack of the nucleophile on the mercury reagent without the usually observed extrusion of CX_2. There is a possibility, as we have pointed out, that such also is the case when phenyl(trihalomethyl)mercurials react with compounds containing the C=N[2,8] and C=S[9] bonds. We indicate both structures III and IV as possibilities since there is

(13) D. Seyferth, J. K. Heeren, G. Singh, S. O. Grim, and W. B. Hughes, *J. Organometal. Chem.*, **5**, 267 (1966).

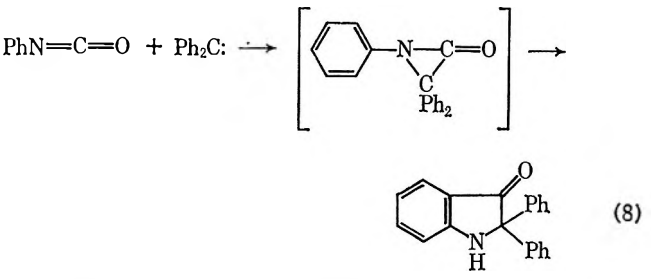
(14) D. Seyferth, M. E. Gordon, and R. Damrauer, *J. Org. Chem.*, **32**, 469 (1967).

no evidence that ring closure takes place in these systems. In the case of compounds containing isolated C=N and C=S bonds, the three-membered heterocyclic rings are formed by $PhHgCCl_2Br$ attack and are stable,[8,9] but in the present cases, in view of the fragmentation processes observed, ring closure is not a necessity.

In the case of phenyl isocyanate, we are dealing with a compound which really is very unreactive toward $PhHgCCl_2Br$. In one experiment in which these compounds were allowed to react, the PhNCO recovery was determined and found to be very high. However, in the case of the other substrates used during this study, the possibility of other reactions proceeding by alternate pathways exists (*e.g.*, *via* the dipolar reagent III which could act as a 1,3 dipole, $^{-}CCl_2—\ddot{Y}—\overset{+}{C}=Z$). To date, however, we have not isolated products other than those mentioned.

These reactions of phenyl(bromodichloromethyl)-mercury cannot be considered to be well understood. However, they appear to have no useful application in synthesis and for this reason we have chosen to discontinue our studies of these systems at this time.

Reactions of three-atom cumulenes with other carbene reagents have been reported, but in these examples the reactions proceeded quite differently. The photochemical reaction of diphenyldiazomethane (believed to proceed *via* diphenylcarbene) took the course shown in eq 8,[15] while the reaction of $(CF_3)_2C$ (*via* the



(8)

diazoalkane or the diazirine) with carbon disulfide at 150–175° gave cyclic polysulfides.[16]

Experimental Section

General Comments.—All reactions with $PhHgCCl_2Br$ were carried out in an atmosphere of prepurified nitrogen or argon in flame-dried glassware using rigorously dried solvents. Nmr spectra were recorded using a Varian Associates A-60 or T-60 spectrometer. Infrared spectra were recorded using a Perkin-Elmer 237B, 337, or 257 grating infrared spectrometer. Gas–liquid partition chromatography (glc) was used routinely for yield determinations and for collections of samples. Commercial stainless steel columns were employed with either an F & M Model 700, 720, or 5754 gas chromatograph. Yields were determined by the internal standard procedure. The standard apparatus used for the reactions of $PhHgCCl_2Br$ with the heteroatom cumulenes consisted of a three-necked flask of appropriate volume equipped with a reflux condenser topped with a gas inlet tube, a thermometer, and a magnetic stirring assembly. Phenyl(bromodichloromethyl)mercury was prepared as described in earlier papers of this series.[17,18] The progress of the reactions involving this reagent was followed using thin layer chromatography.[6]

Reaction of Phenyl(bromodichloromethyl)mercury with Diisopropylcarbodiimide.—The standard apparatus was charged with 3.15 g (25 mmol) of freshly distilled diisopropylcarbodiimide (Eastman), 22.03 g (50 mmol) of the mercurial, and 250 ml of dry chlorobenzene and stirred and heated at 80° for 20 min. A deep yellow mixture resulted. Filtration gave phenylmercuric bromide in 95% yield. Trap-to-trap distillation of the filtrate at 0.1 mm was followed by another distillation at reduced pressure using a small Vigreux column. Each fraction collected (7 total) contained much chlorobenzene, but the later fractions were rich in another major component. This was collected by glc (25% SE-30 silicone rubber gum at 62°) and was identified as *N*-isopropyldichloroimine, $Me_2CHN=CCl_2$. The ir spectrum (in CCl_4) showed bands at 2975 s, 2930 m, 2900 m, 2865 m, 1760 (broad) m, 1660 s, 1645 s, 1470 m, 1460 m, 1380 m, 1370 m, 1340 m, 1290 w, 1175 m, 1130 s, 1035 w, 990 w, 940 w, 880 s, 615 s, and 570 cm^{-1} m; nmr (in CCl_4) δ 1.8 (d, J = 7 Hz, 6, Me_2C) and 3.55–4.05 ppm (m, 1, Me_2CH).

Anal. Calcd for $C_4H_7Cl_2N$: C, 34.32; H, 5.04; N, 10.00; Cl, 50.64. Found: C, 34.15; H, 5.14; N, 10.09; Cl, 50.54.

An authentic sample of this compound, bp 110–114°, $n^{27}D$ 1.4460, was prepared by chlorination (using an excess of chlorine) of isopropyl isothiocyanate in carbon tetrachloride using the procedure of Bly, *et al.*[19] The material obtained was better than 99% pure by glc and its ir spectrum and glc retention time were identical with those of our reaction product.

The earlier fractions of the Vigreux column distillation above contained (by glc) $Me_2CHN=CCl_2$ as major component (in addition to solvent), as well as three minor components. One of these had a glc retention time identical with that of authentic isopropylisonitrile, and a collected sample of the three minor components (preparative glc separation was not feasible) had an ir spectrum which contained all the bands observed in the ir spectrum of $Me_2CHN\equiv C$. The low yield of this product precluded further characterization or yield determination. In further support for the presence of an isonitrile was the unusually pungent odor, characteristic of this class of compounds, which the reaction mixture had.

An authentic sample of isopropylisonitrile was prepared by the method of Ugi, *et al.*:[20] ir (in CCl_4) 2960 s, 2900 s, 2840 m, 2400 w, 2130 s, 2100 m, 2030 w, 1630 w, 1475 s, 1410 s, 1380 s, 1350 s, 1165 s, 1120 (broad) s, 930 w, and 910 cm^{-1} s.

Four reactions between $PhHgCCl_2Br$ and diisopropylcarbodiimide were carried out in C_6H_5Cl solution using the procedure described above, on a small scale and with variations in reagent ratio. Assuming the reaction shown in eq 2, the $Me_2CHN=CCl_2$ yields (by glc) for the following reagent ratios are given.

mmol of $Me_2CHN=C=NCHMe_2$	mmol of $PhHgCCl_2Br$	% yield of $Me_2CHN=CCl_2$
1.00	1.00	66
1.13	1.13	63
1.02	2.04	92
0.95	1.90	92

A reaction carried out using 10 mmol of the carbodiimide and 1 mmol of the mercurial in the hope of increasing the yield of isopropylisonitrile did not achieve the desired result. Again the yield of the latter was very small, and it would appear that the the isonitrile is much more reactive toward the mercurial than is the carbodiimide.

Reaction of Phenyl(bromodichloromethyl)mercury with Dicyclohexylcarbodiimide.—The carbodiimide (0.21 g, 1.0 mmol, Upjohn Co.) and 1 mmol of the mercury reagent in 10 ml of benzene were heated at 73° for 15 min. Filtration gave phenylmercuric bromide in 72% yield. The filtrate was trap-to-trap distilled at 0.05 mm (pot temperature to 80°) and the distillate was analyzed by glc (25% SE-30, 140°). One major component was present. Its infrared spectrum agreed well with that of an authentic sample of cyclo-$C_6H_{11}N=CCl_2$. The latter was prepared by chlorination of cyclohexyl isothiocyanate in 41% yield. Its infrared spectrum (neat liquid) showed bands at 2950 s, 2925 sh, 2865 s, 1780 m, 1725 m, 1660 s, 1650 sh, 1450 m, 1370 m, 1265 w, 1255 w, 1145 w, 1100 (broad) m, 1055 w, 1025 w, 955 m, 905 s, 890 s, 860 s, 790 s, 680 w and 625 cm^{-1} s.

(15) J. C. Sheehan and I. Lengyel, *J. Org. Chem.*, **28**, 3252 (1963).
(16) M. S. Raasch, *ibid.*, **35**, 3470 (1970).
(17) D. Seyferth and J. M. Burlitch, *J. Organometal. Chem.*, **4**, 127 (1965).
(18) D. Seyferth and R. L. Lambert, Jr., *ibid.*, **16**, 21 (1969).
(19) R. S. Bly, G. A. Perkins, and W. L. Lewis, *J. Amer. Chem. Soc.*, **44**, 2896 (1922).
(20) I. Ugi, R. Mayr, M. Lipinski, F. Bodesheim, and F. Rosendahl, *Org. Syn.*, **41**, 13 (1961).

Anal. Calcd for $C_7H_{11}NCl_2$: C, 46.69; H, 6.16. Found: C, 46.57; H, 6.67.

Further work with dicyclohexylcarbodiimide was discontinued when the second author (R. D.) became highly sensitized to the $PhHgCCl_2Br$–dicyclohexylcarbodiimide reaction mixtures. The resulting skin irritations were severe and believed due to the carbodiimide.

Reaction of Phenyl(bromodichloromethyl)mercury with Phenyl Isothiocyanate.—A mixture of 0.70 g (5.0 mmol) of phenyl isothiocyanate and 3.0 g (6.8 mmol) of the mercurial in 10 ml of dry benzene was stirred and heated at 70–75° for 30 min. (*n*-Decane, 1.47 mmol, was present as a glc internal standard.) The reaction mixture was cooled and an aliquot was analyzed by glc (20% DC-200, 135°); the yield of perchlorothiirane was 32%, based on eq 3. Another 6.8 mmol of $PhHgCCl_2Br$ was added to the reaction mixture and heating was continued for another 2 hr. Glc analysis at this time showed that perchlorothiirane was present in 74% yield.

In another experiment, 18.0 mmol of the mercury reagent and 5.0 mmol of phenyl isothiocyanate were mixed all at once in 22 ml of benzene and stirred and heated at 70–75° for 4 hr. The deep brown reaction mixture was filtered to remove 6.3 g of brown, impure phenylmercuric bromide (98%), mp 265–270°. Trap-to-trap distillation of the filtrate at 0.05 mm (pot temperature below 80° for 4 hr, and to 130° for 5 min) was followed by glc analysis of the distillate. Perchlorothiirane was present in 49% yield. This product was identified by comparison of its infrared spectrum and glc retention time with that of an authentic sample obtained by reaction of thiophosgene with $PhHgCCl_2Br$.[9]

When 20.0 mmol of the mercurial and 25.0 mmol of phenyl isothiocyanate in 25 ml of benzene were heated at 70–75° for 4 hr, the usual work-up of the red-brown reaction mixture gave crude phenylmercuric bromide in 96% yield and perchlorothiirane in 59% yield, together with tetrachloroethylene in 2% yield. The latter appears to result from thermolysis of perchlorothiirane; its determined "yield" varied with analysis conditions, being larger when higher column and injection port temperatures were used. Because of the thermal instability of perchlorothiirane, work-up and analysis under the lowest possible temperature conditions is recommended.[21]

N-Phenyldichloroimine was not detected in the glc analyses of these reaction mixtures and in another reaction carried out using 2.25 mmol of $PhHgCCl_2Br$, 0.5 ml of phenyl isothiocyanate, and 3 ml of benzene (3 hr at 81°) a search for higher boiling products (4 ft × 0.25 in., 10% UC W98 at 175°) failed to detect the presence of 1-phenyl-2,2,3,3-tetrachloroaziridine.

Reaction of Phenyl(bromodichloromethyl)mercury with Isopropyl Isothiocyanate.—The mercurial (4.4 g, 10.0 mmol) and the isothiocyanate (1.0 g, 10.0 mmol) in 50 ml of benzene were kept at 30° for 168 hr (with stirring). The reaction mixture turned brown and a brown solid was deposited. The latter, 2.9 g, was mostly phenylmercuric bromide, mp 278–282°. The filtrate was distilled at 0.02 mm (pot temperature to 40°). Analysis of the yellow distillate by glc showed the presence of solvent, a small quantity of tetrachloroethylene, unconverted isopropyl isothiocyanate, and perchlorothiirane (25% yield). *N*-Isopropyldichloroimine was not present.

Reaction of Phenyl(bromodichloromethyl)mercury with Phenyl Isocyanate.—The mercurial (1.0 g, 2.25 mmol) and phenyl isocyanate (3.0 g, 25 mmol) were stirred and heated at 90° for 3 hr. The resulting brown mixture was filtered from 0.75 g (94%) of crude phenylmercuric bromide. Glc analysis (4 ft × 0.25 in., 10% UC W98 on Chromosorb W, 135°) of the trap-to-trap distilled (at 0.02 mm, pot temperature to 100°) filtrate showed the presence of 1-phenyl-2,2,3,3-tetrachloroaziridine in 15% yield. Also present were several minor high-boiling products. The major product was identified by comparison of its infrared spectrum and glc retention time with that of an authentic sample prepared by reaction of $PhHgCCl_2Br$ with $PhN{=}CCl_2$.[8]

A reaction carried out between 5.0 mmol of the mercurial and 25 mmol of phenyl isocyanate in 8 ml of dry benzene at reflux for 3 hr gave the aziridine in 9.2% yield. The yield of crude phenylmercuric bromide was 84%.

A third reaction was carried out in which 10 mmol of $PhHgCCl_2Br$ and 3 ml of phenyl isocyanate were stirred and heated at 85° for 3 hr. The nitrogen sweep gas was passed into a trap containing 30% aqueous ammonia to convert any phosgene that might result from mercurial attack at the C=O bond into urea. Upon completion of the reaction the trap contents were boiled to expel ammonia. An aliquot was concentrated to 0.3 ml and treated with concentrated HNO_3; no precipitate formed. It is concluded that no phosgene had been formed and that the C=O bond of phenyl isocyanate is not involved in the reaction with phenyl(bromodichloromethyl)mercury.

Reaction of Phenyl(bromodichloromethyl)mercury with *trans*-1,2-Diisocyanatoethylene.—The mercurial (7.05 g, 16 mmol) and 1.60 g (14.5 mmol) of *trans*-1,2-diisocyanatoethylene (Aerojet General Corp., mp 67–69°) in 30 ml of dry benzene were stirred and heated at reflux for 2 hr. The light yellow reaction mixture was filtered from 5.34 g (94%) of phenylmercuric bromide, mp 283–286°. Glc analysis of the filtrate (4 ft × 0.25 in., 20% SE-30 at 120°) showed the presence of *trans*-1,2-diisocyanato-3,3-dichlorocyclopropane in 84% yield. A sample was isolated by glc, $n^{25}D$ 1.5138. The nmr spectrum (in CCl_4) showed a singlet at 3.18 ppm. The infrared spectrum (pure liquid) showed bands at 3030 w, 2900 w, 2260 vs, 1760 w, 1475 w, 1370 w, 1300 w, 1190 w, 1062 w, 980 w, 939 w, 903 w and 805 cm^{-1} m.

Anal. Calcd for $C_5H_2Cl_2N_2O_2$: C, 31.11; H, 1.04; Cl, 36.74. Found: C, 31.08; H, 1.22; Cl, 36.20.

Reaction of Phenyl(bromodichloromethyl)mercury with Carbon Disulfide.—A mixture of 0.76 g (10.0 mmol) of carbon disulfide and 11.0 g (25.0 mmol) of the mercurial in 30 ml of benzene was heated at 70–75° for 1 hr. The mixture was filtered from 6.5 g (77%) of phenylmercuric bromide. The red-brown filtrate was trap-to-trap distilled at 0.03 mm (pot temperature below 80°) using 4 g of dodecane as "chaser." Glc analysis (20% DC-200, 135°) showed the presence of perchlorothiirane in 30% yield, based on eq 6.

A second experiment in which 5.0 mmol of carbon disulfide and 27 mmol of the mercurial in 15 ml of benzene were allowed to react at 75–80° for 2 hr gave perchlorothiirane in 27% yield, in addition to a large amount of tetrachloroethylene resulting mostly from the thermolysis of the excess mercurial. The distillation residue in these experiments was a black, benzene- and acetone-soluble tar.

Registry No.—Phenyl(bromodichloromethyl)mercury, 3294-58-4; diisopropylcarbodiimide, 693-13-0; dicyclohexylcarbodiimide, 538-75-0; phenyl isothiocyanate, 103-72-0; isopropyl isothiocyanate, 2253-73-8; phenyl isocyanate, 103-71-9; *trans*-1,2-diisocyanatoethylene, 1441-73-2; carbon disulfide, 75-15-0; *N*-isopropyldichloroimine, 29119-58-2; cyclo-$C_6H_{11}N{=}CCl_2$, 2666-80-0; *trans*-1,2-diisocyanato-3,3-dichlorocyclopropane, 29119-60-6.

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(21) It should be noted that our reported[9] yield of perchlorothiirane as obtained in the $PhHgCCl_2Br$–Cl_2CS reaction, 36% yield, is too low because care was not taken to keep the temperature as low as possible during work-up and analysis. When this was done (W. E. Smith, unpublished), the yield of perchlorothiirane was 96%.

Transfer Reactions Involving Boron. XXII. The Position-Specific Preparation of Dialkylated Ketones from Diazo Ketones and Methyl Vinyl Ketone *via* Vinyloxyboranes[1]

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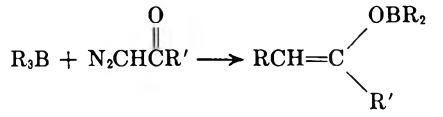
Vinyloxyboranes, formed in the reaction of trialkylboranes with diazo ketones or by the radical addition of trialkylboranes to methyl vinyl ketone, react with methyl- or *n*-butyllithium to form the corresponding lithium enolates and lithium tetraalkylboron. The enolates thus generated undergo facile alkylation in highly position-specific reactions. The overall procedure leads to the formation of α,α- and α,β-dialkylated ketones from diazo ketones and methyl vinyl ketone, respectively, in good yield.

The base-catalyzed alkylation of ketones has received considerable attention. In general, ketones having α hydrogens on both α-carbon atoms undergo base-catalyzed enolate formation at each α position leading to competitive alkylation at both α positions. House and coworkers[3] have shown that enolates do not equilibrate unless there is a hydrogen ion donor available in the reacting system. The product-alkylated ketones are capable of acting as the hydrogen ion donor, thus leading to the equilibration of enolates, as well as the polyalkylation of the initial ketone. Numerous procedures have been developed to circumvent alkylation at both α positions and the polyalkylation of ketones. These procedures have involved the use of blocking and activating functional groups,[4] the position-specific formation of enolates by reduction of α,β-unsaturated ketones[5] or α-substituted ketones,[5,6] and the formation, trapping, separation, and regeneration of enolates.[7-9]

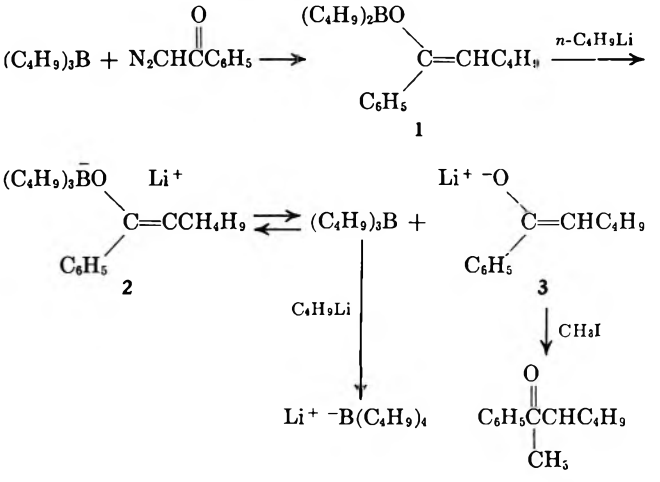
House and Trost[7] have described the cleavage of enol acetates with methyllithium to give enolates which could then be alkylated in a high degree of position specificity. The pure enol acetates were prepared by the reaction of the sodium enolates, formed by the reaction of the ketones with sodium hydride, with acetic anhydride followed by separation by preparative glpc. Stork and Hudrlik[8] have described similar procedures for the generation of enolates from methyllithium and trimethylsilyl enol ethers (again requiring the separation of the isomeric enol ethers by preparative glpc or fractional distillation). Pereyre and coworkers have described the preparation of tin enol ethers by the radical addition of trialkyltin hydride to α,β-unsaturated ketones.[9a,b] Subsequent cleavage of the tin enol ethers with methyllithium leads to the formation of lithium enolates which can be alkylated.[9c,d,e]

Our recent observation that vinyloxyboranes are formed in the reactions of trialkylboranes with diazo ketones[10] has led us to investigate the utilization of such intermediates for the generation of enolates followed by alkylation.



Results and Discussion

The reaction of diazoacetophenone with tri-*n*-butylboron in dry tetrahydrofuran produces the vinyloxyborane **1**.[10] Direct treatment of crude **1** with 2 molar equiv of *n*-butyllithium in hexane followed by the addition of 1 molar equiv of methyl iodide produces an overall 72% yield of 2-hexyl phenyl ketone. The use of less than 2 molar equiv of *n*-butyllithium results in lower yields of the dialkylated product. We picture the reaction as involving attack by *n*-butyllithium on **1** to



form the tetracoordinate boron species **2** which reversibly dissociates to tri-*n*-butylboron and the lithium enolate. The second equivalent of *n*-butyllithium presumably assists in the formation of the free enolate by irreversibly removing the tri-*n*-butylboron as lithium tetra-*n*-butylboron.[11] The lithium tetrabutylboron formed in the reaction does not react with the product ketones at room temperature over the course of several

(1) Submitted by P. W. W. in partial fulfillment of the requirements for the Ph.D. thesis, University of Notre Dame, 1971.

(2) (a) Alfred P. Sloan Research Fellow, 1967–1969; (b) NDEA Fellow, 1967–1970.

(3) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

(4) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965.

(5) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(6) D. Caine, *J. Org. Chem.*, **29**, 1868 (1964).

(7) H. O. House and B. M. Trost, *ibid.*, **30**, 2502 (1965).

(8) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4464 (1968).

(9) (a) M. Pereyre and J. Valade, *Bull. Soc. Chim. Fr.*, 1928 (1967); (b) M. Pereyre, B. Bellegarde, J. Mendelsohn, and J. Valade, *J. Organometal. Chem.*, **11**, 97 (1968); (c) M. Pereyre and Y. Odic, *Tetrahedron Lett.*, 505 (1969); (d) Y. Odic and M. Pereyre, *C. R. Acad. Sci., Ser. C*, **269**, 469 (1969); (e) Y. Odic and M. Pereyre, *ibid.*, **270**, 100 (1970).

(10) D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, 215 (1970).

(11) Lithium and sodium tetraalkylboron compounds have been prepared previously.[12] These compounds are reported to undergo rather slow hydrolysis and air oxidation (0.5–16% hydrolysis in water at room temperature for 16 hr and 50% oxidation in tetrahydrofuran at 35° for 16 hr[12]). These compounds are considerably less reactive than lithium tetramethylaluminum toward hydrolysis, oxidation, and reaction with aldehydes and ketones.[13]

(12) R. Damico, *J. Org. Chem.*, **29**, 1971 (1964).

(13) D. J. Pasto and R. Snyder, *ibid.*, **30**, 1634 (1965).

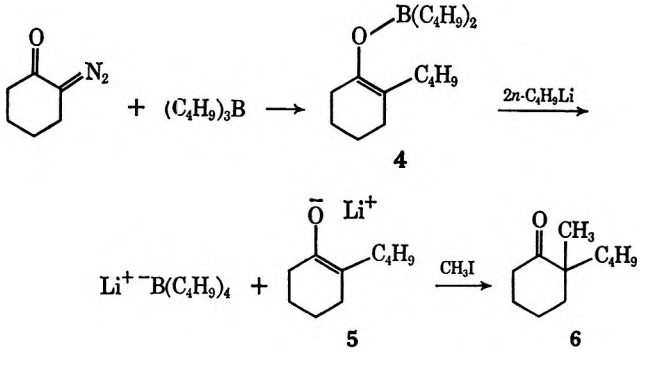
hours as demonstrated in a control reaction of a ketone with lithium tetrabutylboron (prepared by the reaction of *n*-butyllithium with tri-*n*-butylboron[12]).

The enolate **3** can also be generated from **1** using methyllithium or potassium *tert*-butoxide, although in the latter case considerably lower yields of dialkylated product are obtained. Enolate **3** was also reacted with 1 molar equiv of benzyl chloride giving 1-phenyl-2-hexyl phenyl ketone in 47% yield. In the alkylation reactions involving **3**, no polyalkylation products were detected. The results of the reactions of vinyloxyborane **1** with different bases and alkylating agents are summarized in Table I.

TABLE I
ALKYLATION OF ENOLATE ANION DERIVED FROM 1

Base (molar equiv)	Alkylating agent	Yield, %
n-C_4H_9Li (2)	CH_3I	72
n-C_4H_9Li (1)	CH_3I	56
CH_3Li (2)	CH_3I	69
n-C_4H_9Li (2)	$C_6H_5CH_2Cl$	47
K^+ $^-$O-*tert*-Bu (1)	$C_6H_5CH_2Cl$	31

In the foregoing system only a single enolate anion can be formed. A more challenging problem which has received considerable attention is the selective generation of a single enolate anion from an unsymmetrical acyclic or cyclic ketone, which can potentially form two different, isomeric enolate anions, followed by the position-specific alkylation of that enolate anion. We have investigated the utility of the present procedure with both an unsymmetrical acyclic and cyclic system.[14] Reaction of diazocyclohexanone[15] with tri-*n*-butylboron in dry tetrahydrofuran led to the formation of vinyloxyborane **4**. Treatment of crude **4** with *n*-butyllithium in hexane followed by the addition of methyl iodide produced only low and variable yields of the desired product **6**. Removal of the tetrahydrofuran from crude **4** followed by distillation of **4** under a nitrogen atmosphere and subsequent treatment with *n*-butyllithium and methyl iodide produced **6** in 61%

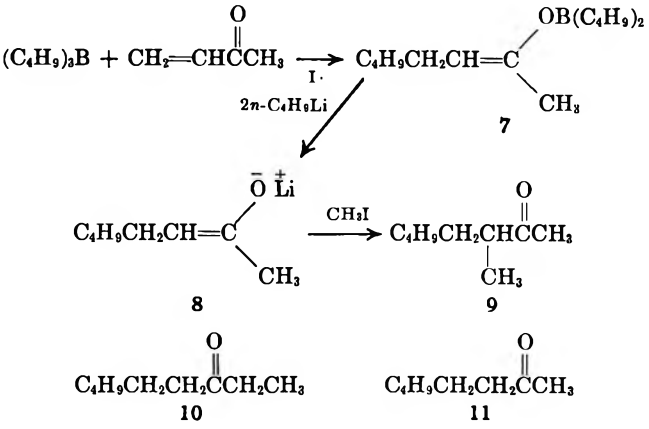


yield. Analysis of the reaction product by glpc and mass spectrometry indicated the presence of a few per cent of 2-*n*-butylcyclohexanone and no more than trace quantities of polymethylation products. The presence of the isomeric alkylation product, 2-methyl-6-*n*-butylcyclohexanone, could not be detected by glpc.

(14) L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith, *J. Org. Chem.*, **35**, 1881 (1970), and references contained therein. See also ref 8.

(15) M. Rosenberger, P. Yates, J. B. Hendrickson, and W. Wolf, *Tetrahedron Lett.*, 2285 (1964).

The reaction of crude vinyloxyborane **7**,[10] formed by the conjugate radical addition of tri-*n*-butylboron to methylvinyl ketone,[16] with *n*-butyllithium followed by the addition of methyl iodide produced only low yields of the expected alkylation product **9**. As with **4**, distillation of **7** followed by the treatment with *n*-butyllithium and methyl iodide produced the expected product **9** in reasonable yield (59%), in addition to **10** (11%), **11** (10%), and approximately 3% of unidentified polyalkylated products (by mass spectral analysis). The



formation of **10** and the polyalkylation products from **8** is not atypical. It is well documented that acyclic enolate anions such as **8** lose both their position specificity and undergo polyalkylation to a greater extent than cyclic enolate anions such as **5**.[14]

The formation of position-specific alkylated ketones from diazo ketones and methyl vinyl ketone *via* vinyloxyboranes appears to be advantageous over the other methods of enolate anion formation in that only one positional isomer of the vinyloxyborane is formed, thus precluding the necessity of separation of the enol derivatives prior to enolate anion generation. The ready availability of acyclic diazo ketones (from acid chlorides with diazoalkanes), methyl vinyl ketone, and trialkylboranes (by hydroboration of olefins) provides for a rather flexible synthetic approach to the preparation of ketones of various structures. These facts, coupled with the fact that vinyloxyboranes can be prepared in large quantities, allow for a *smooth position-specific introduction of two alkyl groups* in a single sequence of reactions starting from simple and readily available precursors.

Experimental Section

Dialkylation of Diazoacetophenone. A. Preparation of 2-Hexyl Phenyl Ketone.—To a cooled (0°) solution of 6.35 mmol of di-*n*-butyl-(1-phenyl-1-hexenyloxy)borane (**1**) in 10 ml of tetrahydrofuran, prepared by the reaction of 6.35 mmol of diazoacetophenone with 6.35 mmol of tri-*n*-butylboron in tetrahydrofuran, was added dropwise 6.6 ml of 1.92 *M* (12.7 mmol) methyllithium in diethyl ether (or the other bases as indicated in Table I). The ice bath was removed and the reaction mixture was allowed to stir for 1 hr at room temperature. Methyl iodide (6.35 mmol) was added and the reaction mixture was allowed to stir for 90 min. The reaction mixture was diluted with ether and was repeatedly washed with water. The organic phase was dried over magnesium sulfate and the solvent was removed under reduced pressure. Analysis of the residue by glpc indicated the presence of only 2-hexyl phenyl ketone (69%). The residue was subjected to distillation giving pure product: bp 115° (3.3 mm)

(16) A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogic, and M. W. Rathke, *J. Amer. Chem. Soc.*, **89**, 5708 (1967).

[lit.[17] bp 109–111° (3 mm)]; ν_{max} 1682 cm^{-1}; nmr δ 0.6–2.0 (m, 9 H), 1.7 (d, J = 7.0 Hz, 3 H), 3.33 (m, 1 H), and 7.35 and 7.96 (m, 5 H each).

B. Phenyl 1-Phenyl-2-hexyl Ketone.—Treatment of the enolate 3 with benzyl chloride followed by work-up as described above produced phenyl 1-phenyl-2-hexyl ketone (for yields see Table I): bp 145° (0.55 mm); ν_{max} 1675 cm^{-1}; nmr δ 0.6–2.0 (m, 9 H), 2.91 (m, 2 H), 3.70 (m, 1 H), and 7.1–7.8 (m, 10 H). The product was identical in all respects with an authentic sample prepared by the benzylation of the enolate anion of caprophenone generated by treatment of caprophenone with sodium hydride in monoglyme.

Dialkylation of Diazocyclohexanone. Preparation of 2-Methyl-2-*n*-butylcyclohexanone.—To a solution of 1.82 g (14.7 mmol) of diazocyclohexanone[15] in 2 ml of tetrahydrofuran maintained under a nitrogen atmosphere was added 2.68 g (14.7 mmol) of tri-*n*-butylboron in 2 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was distilled under a nitrogen atmosphere giving 2.83 g (70%) of 4 as a pale yellow liquid: bp 97° (0.32 mm); ν_{max} 1687 cm^{-1} ($\nu_{C=C}$) with no absorption in the carbonyl region. The distillate was dissolved in 5 ml of tetrahydrofuran and the solution was cooled in an ice bath. A solution of *n*-butyllithium in hexane (20.8 mmol) was added dropwise and the resulting reaction mixture was allowed to stir at room temperature for 1 hr. Methyl iodide (2.9 g, 20.8 mmol) was then added and the reaction mixture was stirred for 30 min and was then worked up as described above. Analysis of the product by glpc indicated the presence of 2-methyl-2-*n*-butylcyclohexanone (61%) and 2-*n*-butylcyclohexanone[18] (6%). The 2-methyl-2-*n*-butylcyclohexanone was isolated by preparative glpc, ν_{max} 1705 cm^{-1}. The 2,4-dinitrophenylhydrazone had mp 140–141° (lit.[19] mp 139–140°).

Dialkylation of Methyl Vinyl Ketone. Preparation of 3-Methyl-2-octanone.—To a solution of 3.59 g (15.1 mmol) of 7 in 9 ml of tetrahydrofuran maintained at 0° was added dropwise 11.3 ml of 2.67 *M* (30.2 mmol) *n*-butyllithium in hexane. The reaction mixture was allowed to stir at room temperature for 1 hr. A solution of 4.29 g (30.2 mmol) of methyl iodide in 1 ml of tetrahydrofuran was added and the resulting mixture was stirred at room temperature for 30 min, whereupon the reaction mixture was worked up as described above. Analysis of the product mixture by glpc showed the presence of 3-methyl-2-octanone (59%), 3-nonanone (16%), 2-octanone (10%), and 3% of unidentified products. The 3-methyl-2-octanone was isolated by preparative glpc: ν_{max} 1710 cm^{-1}; nmr δ 0.7–1.8 (m, 14 H), 2.12 (s, 3 H), and 2.47 (m, 1 H); mass spectrum *m/e* 142, 127, 99, 72.

Registry No.—1, 29128-31-2; 4, 29199-34-6; 7, 29199-35-7; diazoacetophenone, 3282-32-4; tri-*n*-butylboron, 122-56-5; diazocyclohexanone, 3242-56-6; methyl vinyl ketone, 78-94-4.

(17) T. I. Temnikova, A. K. Petryaeva, and S. S. Skorokhodov, *Zh. Obshch. Khim.*, **25**, 1575 (1955).

(18) Identified by comparison with an authentic sample obtained by the hydrolysis of vinyloxyborane 4.

(19) S. Boatman, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 82 (1965).

Enthalpies of Transfer of Transition States in the Menshutkin Reaction from a Polar Protic to a Dipolar Aprotic Solvent[1]

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The rates of the reaction of pyridine with six benzyl halides in methanol and dimethylformamide (DMF) were determined at 25.0 and 50.0°. The heats of solution of the reactants in these two solvents were determined at 25.0°. From these data the enthalpies of transfer of the transition states of these reactions from methanol to dimethylformamide were calculated. In all cases the lower activation enthalpy in the dipolar aprotic solvent was found to be caused *entirely* by greater solvation of the transition state in the dipolar aprotic solvent rather than by solvation effects on the reactants. Some effects upon this transition state of changes in the leaving group and in the substrate are discussed.

The Menshutkin reaction has long been regarded as one of the best examples of solvent effects upon reaction rate. Since ions are formed from neutral reactants in this reaction, large increases in rate have been observed with increases in the polarity of the solvent.[3] In addition to correlation of rates with dielectric constant,[4] Z values,[5] and polarizability,[6] it appears that there is an interesting effect on change from a polar protic to a dipolar aprotic solvent of similar dielectric constant.

The effect of this solvent change on the free energies of activation of SN2 reactions has been the subject of thorough studies by Parker and coworkers,[7] and, in the case of the Menshutkin reaction, by Abraham.[3b] These authors discuss this solvent effect in terms of the free energy of transfer of the transition state in these reactions from a polar protic to a dipolar aprotic solvent. Another variable, namely the solvent effect on the volume of activation of the Menshutkin reaction, has been studied by Brower.[8]

Although the effect on rate of a change from a polar protic to a dipolar aprotic solvent is not great and both rate increases[9] and rate decreases[9,10] have been reported, there does seem to be a consistent decrease in the enthalpy of activation in the dipolar aprotic solvent.[9,10] This decrease in the $\Delta H^{\pm}$ can be attributed to two possible causes.

The first, and most common, explanation is that desolvation of the nucleophile or base in the aprotic solvent relative to the protic solvent raises the energy of the reactants, thus diminishing the energy gap between the reactants and the transition state. The second explanation is that the lowering of the activation energy

(1) (a) A preliminary report of a part of this work appeared in *Chem. Commun.*, 194 (1968). (b) This work was supported in part by the National Science Foundation under its Undergraduate Science Education Program, 1963–1965.

(2) Taken in part from the M. A. thesis of A. Nudelman, Brooklyn College, Feb 1964.

(3) (a) N. Menschutkin, *Z. Phys. Chem.*, **5**, 589 (1890); (b) for a more recent discussion, see M. H. Abraham, *Chem. Commun.*, 1307 (1969).

(4) S. Eagle and J. Warner, *J. Amer. Chem. Soc.*, **61**, 488 (1939).

(5) E. M. Kosower, *ibid.*, **80**, 3267 (1958).

(6) J. D. Reinheimer, J. D. Harley, and W. W. Meyers, *J. Org. Chem.*, **28**, 1575 (1963).

(7) E. C. F. Ko and A. J. Parker, *J. Amer. Chem. Soc.*, **90**, 6447 (1968), and earlier papers.

(8) K. R. Brower, *ibid.*, **85**, 1401 (1963); see also H. Heydtman, *Z. Phys. Chem.*, **54**, 237 (1967).

(9) (a) J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 519 (1935); (b) B. O. Coniglio, D. E. Giles, W. R. McDonald, and A. J. Parker, *J. Chem. Soc., B*, 152 (1966).

(10) H. Essex and O. Gelomini, *J. Amer. Chem. Soc.*, **48**, 883 (1926).

is caused by increased solvation of the transition state in the dipolar aprotic solvent. A combination of both effects is also conceivable. A direct means of distinguishing between these possibilities, as demonstrated in the work of Arnett,[11] is to determine the difference in the enthalpies of activation of a reaction in a pair of solvents, $\delta\Delta H^{\ddagger}$, and to compare them to the enthalpies of transfer of the reactants from one solvent to the other, $\delta\Delta H_s$.

The decrease in the $\Delta H^{\ddagger}$ for the Menshutkin reaction on going from a polar protic to a dipolar aprotic solvent is quite large and is of the same order of magnitude as that observed for SN2 reactions having a negatively charged nucleophile and a neutral electrophile.[9,12] Recently we were able to show[13] that for some SN2 reactions of this second type the decrease in $\Delta H^{\ddagger}$, which accompanies the very large rate enhancement of these reactions in dipolar aprotic solvents, was caused principally by increased solvation of the transition state rather than by decreased solvation of the nucleophile in the dipolar aprotic solvent. This was particularly true when the nucleophile was a *weak* base.

The purpose of the present work was to measure the dipolar aprotic solvent effect for the Menshutkin reaction as a function of leaving group and substrate variation and to determine to what degree the effect upon the $\Delta H^{\ddagger}$ in each particular case was caused by an effect on the enthalpies of solvation of the reactants and of the transition state. For this purpose we chose methanol and dimethylformamide (DMF), two solvents having very similar dielectric constants, in order to focus, as much as possible, solely upon the differences between a protic and a dipolar aprotic solvent.

Results and Discussion

The solvent effect upon the rates of reaction of six benzyl halides with pyridine can be seen in Table I. There is a substantial rate enhancement by the dipolar aprotic solvent on the rates of the bromides but none on the rates of the chlorides. The rate-enhancing effect is increased by an electron-withdrawing group and diminished by an electron-donating group. The thermodynamic activation parameters are listed in Table II. A plot of $\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$ for the chlorides in each solvent and for the bromides in each solvent yielded four parallel lines with an isokinetic temperature of 355°K. The rate increases are reflected in a substantial lowering of the $\Delta H^{\ddagger}$ in DMF; however, this effect is even more pronounced for the chlorides than for the bromides. Again the effect is increased by an electron-withdrawing group and diminished by an electron-donating group.

To determine whether the effect is caused by a lowered enthalpy of the transition state in DMF or by a lower enthalpy of the reactants in methanol, we determined the enthalpy of transfer of the reactants from methanol to DMF. Table III contains the heats of solution, ΔH_s, of the reactants in the two solvents measured at the concentration at which the kinetic measurements were made and the enthalpy of transfer, $\delta\Delta H_s$, of the reactants from methanol to DMF. As can be seen, the endothermic $\delta\Delta H_s$ of pyridine from methanol to DMF (attributable to H bonding by methanol to the nucleophile) is cancelled by approximately equal exothermic $\delta\Delta H_s$ values for the benzyl halides (except for the nitro compounds where this effect is about twice as large). Thus the total $\delta\Delta H_s$ of the reactants from the one solvent to the other is nearly zero (except for the nitro compounds where the reactants actually have a slightly higher enthalpy in methanol than in DMF). The enthalpy of transfer of a transition state from one solvent to another, δH^t, is obtained from the relation $\delta H^t = \delta\Delta H_s + \delta\Delta H^{\ddagger}$, where $\delta\Delta H_s$ is the enthalpy of transfer of the reactants from one solvent to the other and $\delta\Delta H^{\ddagger}$ is the difference in the activation enthalpies

TABLE I

RATE CONSTANTS FOR THE REACTION OF PYRIDINE WITH VARIOUS BENZYL HALIDES IN METHANOL AND DIMETHYLFORMAMIDE AT 25.0 AND 50.0°

Benzyl halide	Solvent	Temp, °C	k_2[a] × 10^5 l. mol^{-1} sec^{-1}
p-Nitrobenzyl chloride	Methanol	25.0	0.122
		50.0	3.10
	DMF	25.0	0.251
		50.0	2.64
Benzyl chloride	Methanol	25.0	0.346
		50.0	4.39
	DMF	25.0	0.374
		50.0	2.37
p-Methylbenzyl chloride	Methanol	25.0	0.820
		50.0	7.95
	DMF	25.0	0.950
		50.0	5.62
p-Nitrobenzyl bromide	Methanol	25.0	4.91
		50.0	44.7
	DMF	25.0	58.4
		50.0	348
Benzyl bromide	Methanol	25.0	9.64
		50.0	55.5
	DMF	25.0	84.6
		50.0	394
p-Methylbenzyl bromide	Methanol	25.0	27.8
		50.0	151
	DMF	25.0	128
		50.0	569

[a] Standard deviations were generally within ±4%.

TABLE II

ACTIVATION PARAMETERS[a] FOR THE REACTION OF BENZYL HALIDES WITH PYRIDINE IN METHANOL AND DIMETHYLFORMAMIDE

Benzyl halide	Solvent	$\Delta H^{\ddagger}$,[b] kcal mol^{-1}	$\Delta S^{\ddagger}$,[b] mol^{-1} deg^{-1}	$\delta\Delta H^{\ddagger}$,[c] kcal mol^{-1}
p-Nitrobenzyl chloride	Methanol	24.1	−4.45	
	DMF	17.3	−25.6	−6.8
Benzyl chloride	Methanol	18.8	−20.1	
	DMF	13.5	−37.7	−5.3
p-Methylbenzyl chloride	Methanol	16.7	−25.3	
	DMF	13.0	−37.7	−3.7
p-Nitrobenzyl bromide	Methanol	16.2	−23.4	
	DMF	13.0	−29.3	−3.2
Benzyl bromide	Methanol	12.8	−33.8	
	DMF	11.1	−34.8	−1.7
p-Methylbenzyl bromide	Methanol	12.3	−34.6	
	DMF	10.9	−34.8	−1.4

[a] At 25.0°. [b] $\Delta H^{\ddagger}$, ±0.6 kcal mol^{-1}; $\Delta S^{\ddagger}$, ±1.5 cal mol^{-1} deg^{-1} or better. [c] $\delta\Delta H^{\ddagger} = \Delta H^{\ddagger}$ in DMF − $\Delta H^{\ddagger}$ in methanol.

(11) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. M. Duggleby, *J. Amer. Chem. Soc.*, **87**, 1541 (1965).

(12) N. Tokura and Y. Kondo, *Bull. Chem. Soc. Jap.*, **37**, 133 (1964).

(13) P. Haberfield, L. Clayman, and J. Cooper, *J. Amer. Chem. Soc.*, **91**, 787 (1969).

TABLE III

HEATS OF SOLUTION OF BENZYL HALIDES AND PYRIDINE IN METHANOL AND DIMETHYLFORMAMIDE AT 25°

Reagent	ΔH_s (CH_3OH), kcal/mol	ΔH_s (DMF), kcal/mol	$\delta\Delta H_s$,[a] kcal/mol
p-Nitrobenzyl chloride	5.97	4.16	−1.81
Benzyl chloride	0.44	−0.39	−0.83
p-Methylbenzyl chloride	0.60	−0.26	−0.86
p-Nitrobenzyl bromide	7.03	4.72	−2.31
Benzyl bromide	0.76	−0.44	−1.20
p-Methylbenzyl bromide	5.12	4.17	−0.95
Pyridine	−0.95	−0.09	0.86

[a] The enthalpy of transfer from methanol to DMF, $\delta\Delta H_s = \Delta H_s$ (DMF) − ΔH_s (CH_3OH); standard deviations were generally within 0.05 kcal/mol.

of the reaction in the two solvents. Table IV lists these quantities for the six Menshutkin reactions which we have examined.

TABLE IV

ENTHALPIES OF TRANSFER (δH^t) OF THE TRANSITION STATES IN THE MENSHUTKIN REACTION FROM METHANOL TO DIMETHYLFORMAMIDE

Reaction	$\delta\Delta H_s$, kcal/mol	$\delta\Delta H^{\pm}$, kcal/mol	δH^t, kcal/mol
Pyridine + *p*-nitrobenzyl chloride	−0.95	−6.8	−7.8
Pyridine + benzyl chloride	0.03	−5.3	−5.3
Pyridine + *p*-methylbenzyl chloride	−0.00	−3.7	−3.7
Pyridine + *p*-nitrobenzyl bromide	−1.45	−3.2	−4.7
Pyridine + benzyl bromide	−0.34	−1.7	−2.0
Pyridine + *p*-methylbenzyl bromide	−0.09	−1.4	−1.5

The most important conclusion to be drawn from these data is that the very substantial decreases in the enthalpy of activation for the Menshutkin reaction on going from a polar protic to a dipolar aprotic solvent are caused *entirely* by enhanced solvation of the transition state in the dipolar aprotic solvent and not by desolvation of the reactants. Several other observations can be made.

(1) It is interesting that the dipolar aprotic rate enhancement effect is greater for bromides than for chlorides, whereas the dipolar aprotic $\Delta H^{\pm}$ lowering is greater for chlorides than for bromides. The lack of rate enhancement for the chlorides appears to be caused by a very high negative entropy of activation for the reaction in DMF relative to that in methanol (Table II). This may be caused by a more tight transition state in DMF, a medium providing no H-bonding stabilization to the leaving group. This lack of stabilization for the leaving group would be more important for Cl^- than for Br^-.

Another,[9b] more obvious, explanation for the rate effect, namely that the transition state is well solvated by hydrogen-bonding interactions with methanol and that these interactions would be stronger for Cl than for Br, is inconsistent with the $\delta\Delta H^{\pm}$ and $\delta\Delta S^{\pm}$ values. These clearly indicate that there is a decrease in the $\Delta H^{\pm}$ in DMF for both halides which is, however, vitiated by an unfavorable change in the $\Delta S^{\pm}$ values on going to DMF in the case of the chlorides. Abraham[3b] has shown that in the reaction of trimethylamine with *p*-nitrobenzyl chloride the rate enhancement in a dipolar aprotic solvent was caused by transition state stabilization in the dipolar aprotic solvent, *i.e.*, that $\delta\Delta G^{\pm} = \delta G^t$. Since we have shown that for our reactions $\delta\Delta H^{\pm} = \delta H^t$ this suggests that $\delta\Delta S^{\pm} = \delta S^t$. The lack of rate enhancement of benzyl chlorides in DMF is then clearly a consequence of an unfavorable entropy of transfer of the transition state from methanol to DMF rather than greater stabilization of the transition state in methanol than in DMF.

The rule of Swain and Thornton,[14] applied to our reactions, predicts the tightest transition state for *p*-nitrobenzyl chloride. This is the reaction for which we find our most negative $\delta\Delta S^{\pm}$ value. This suggests that the compound which is predicted to have the least bond breaking in the SN2 transition state is most sensitive to a solvent effect which tightens that transition state.

(2) Electron withdrawal at the central carbon increases the rate enhancement as well as the $\Delta H^{\pm}$ lowering by the dipolar aprotic solvent. We believe that this is caused by a shift toward products in the transition state structure.[15] In the Menshutkin reaction this would mean a more dipolar transition state and hence one having the greatest degree of solvation by a dipolar aprotic solvent.

(3) Although the enthalpies of transfer of the transition states from methanol to DMF (δH^t's) are all exothermic, there is a very considerable variation in the values (from −1.5 to −7.8 kcal/mol). We see this mainly as a consequence of a continuous shift toward products in transition state structure with increasing exothermicity of the δH^t values. The transition states which are furthest along the reaction coordinate have the greatest degree of dipolar character and are therefore best solvated by a dipolar aprotic solvent.[16]

(4) SN2 transition states having a net zero charge (Menshutkin reaction) and those having a net negative charge[13] both appear to have large exothermic δH^t values from methanol to DMF, but only the second type show large rate enhancements in the dipolar aprotic solvent. This seems to be the consequence of a much more negative δS^t (from methanol to DMF) for the neutral transition states than for the negatively charged ones.

Experimental Section

Materials.—Dimethylformamide was dried over anhydrous P_2O_5, decanted, and distilled using a 90-cm, glass helix packed column at 12-mm pressure. Methanol was distilled from magnesium. Pyridine (Baker) was dried over KOH and distilled, $n^{20}D$ 1.5092. Benzyl chloride (Baker) was decanted from anhydrous $NaHCO_3$ and distilled at reduced pressure, $n^{15}D$ 1.5416. Benzyl bromide (Eastman) was decanted from anhydrous Na_2CO_3 and fractionated at reduced pressure, $n^{20}D$ 1.5757. *p*-Methylbenzyl chloride was decanted from anhydrous Na_2CO_3 and fractionated, $n^{20}D$ 1.5323. *p*-Methylbenzyl bromide was sublimed at reduced pressure, mp 38.0–38.7°. *p*-Nitrobenzyl chloride was recrystallized from benzene, mp 73.0–73.5°. *p*-

(14) C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **84**, 217 (1962).

(15) Such a substituent effect on the transition state structure is predicted by the rules suggested by J. C. Harris and J. L. Kurz, *ibid.*, **92**, 349 (1970). These authors predict that an electron-withdrawing substituent will have a bond-strengthening effect on the nucleophile and a bond-weakening effect on the leaving group, whereas the Swain–Thornton rule predicts a bond-strengthening effect on both the entering and the leaving groups.

(16) In the case of the nitro compounds, it is useful to consider a contribution to the δH^t value by the NO_2 group itself, aside from its influence on the transition state of complex. This way of looking at it can be justified by the large exothermic enthalpies of transfer of the reactants, *p*-nitrobenzyl chloride and *p*-nitrobenzyl bromide. Another example of the affinity of a dipolar aprotic solvent for molecules having nitro groups is the $\delta\Delta H_s$ (methanol to DMF) of 2,4-dinitrochlorobenzene which is −3.45 kcal/mol.[11]

Nitrobenzyl bromide was recrystallized from benzene, mp 98.0–98.7°.

Rates.—The concentrations of reactants ranged from 0.02 to 0.50 *M*. The concentration of the benzyl halide was equal to that of pyridine in each run. Rates were determined by following the disappearance of base or the appearance of halide ion. In some instances both methods were employed for the same reaction to provide an added check. The base concentration was determined by titration with perchloric acid in glacial acetic acid solvent. To determine the halide concentration, an aliquot of the reaction mixture was added to a mixture of ice water and ligroin in a separatory funnel. After two countercurrent washings, the aqueous phases were titrated for halide using the Volhard method. The second-order rate constants obtained in the usual manner invariably showed an upward drift. We attributed this to concurrent solvolysis in most cases and therefore treated our data by the method reported by Young and Andrews.[17] The yields and melting points of the products were determined for most runs at 25.0° and are listed in Table V.

Heats of Solution.—The calorimeter vessel was a 250-ml dewar flask, 11 cm deep and 6-cm i.d., equipped with a rubber stopper and placed within a styrofoam box for added insulation. The stopper had five holes drilled into it to accommodate the following items: a 24.0–26.0°, 30-cm-long thermometer (Brooklyn Thermometer Co.); a stirrer passing through a bushing made of a ball and socket joint, made from a 3-mm glass rod shaped into a 3-cm propeller pitched to drive liquid downward and attached to a stirring motor; two pieces of 16-gauge copper wire joined at the bottom by a 3-cm length of 38-gauge Nichrome-V wire; an 8-cm-o.d. length of glass tubing ending in a fragile glass bulb, containing the solute and a glass breaker rod passing through a rubber septum at the top.

After 200 ml of solvent was placed into the dewar flask, the apparatus was assembled and temperature readings were taken at 30-sec intervals until a steady base line was established. The glass breaker rod was now pushed through the fragile glass bulb containing the solute, the ensuing rise or fall of temperature times the heat capacity being the heat of solution. The heat capacity of the calorimeter was now determined by passing current through the heater for 15 or 30 sec, using two cells of a lead storage battery as the current source. The voltage drop across the heater was measured during the heating period and the resistance of the heater was determined before and after a run. The amount of electrical energy supplied divided by the temperature rise was the heat capacity of the system. When the calorimeter was tested by measuring the heat of solution of KCl in water, the literature value was duplicated with an average deviation of 30 cal/mol. The concentration of solute employed ranged from 0.01 to 0.1 *M*.

TABLE V

YIELDS AND MELTING POINTS OF PRODUCTS FOR RATES AT 25.0°

Product	Solvent	Yield, %	Mp, °C[a]
p-Nitrobenzylpyridinium chloride	Methanol	>96	211–213[b]
	DMF	>96	
Benzylpyridinium chloride	Methanol	98	127–129
	DMF	96	
p-Methylbenzylpyridinium chloride	Methanol	94	
	DMF		
p-Nitrobenzylpyridinium bromide	Methanol	>98	226–228[c]
	DMF	>98	
Benzylpyridinium bromide	Methanol	97	110–111[d]
	DMF	93	
p-Methylbenzylpyridinium bromide	Methanol	96	123–124
	DMF		

[a] All melting points are uncorrected and are for recrystallized samples. [b] Lit. mp 207° [C. G. Raison, *J. Chem. Soc.*, 2070 (1949)]. [c] Lit. mp 218–219° [F. Kröhnke and K. Ellegant, *Chem. Ber.*, **86**, 1556 (1953)]. [d] Lit. mp 110–111° [J. A. Berson, E. M. Evleth, Jr., and Z. Hamlet, *J. Amer. Chem. Soc.*, **87**, 2887 (1965)].

Registry No.—Pyridine, 110-86-1; *p*-nitrobenzyl chloride, 100-14-1; benzyl chloride, 100-44-7; *p*-methylbenzyl chloride, 104-82-5; *p*-nitrobenzyl bromide, 100-11-8; benzyl bromide, 100-39-0; *p*-methylbenzyl bromide, 104-81-4; benzylpyridinium chloride, 2876-13-3; *p*-methylbenzylpyridinium bromide, 29182-75-0.

(17) (a) W. G. Young and L. J. Andrews, *J. Amer. Chem. Soc.*, **66**, 421 (1944); (b) N. K. Vorobev and G. F. Titova [*Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.*, **9** (2), 218 (1966); *Chem. Abstr.*, **65**, 12074*g* (1966)] also report an upward drift in the second-order rate constant for the reaction of benzyl bromide with pyridine in methanol and report a rate constant at 25° of $k_2 = 20.5 \times 10^{-5}$ l. mol^{-1} sec^{-1}. This compares with a value of $k_2 = 17.7 \times 10^{-5}$ l. mol^{-1} sec^{-1} which we obtain by extrapolating our apparent second-order rate constant to zero time but, of course, does not agree with the k_2 calculated by the method of Young and Andrews. It is gratifying to note that the same reaction in DMF, where solvolysis should be less important, gives similar values for both methods of calculation, namely 84.6×10^{-5} l. mol^{-1} sec^{-1} (our data, method of calculation of Young and Andrews), 73.9×10^{-5} l. mol^{-1} sec^{-1} (our data, extrapolation of apparent k_2 to zero time), and 79.2×10^{-5} l. mol^{-1} sec^{-1} (Vorobev and Titova).

Mass Spectrometry in Structural and Stereochemical Problems. CCII.[1] Interaction of Remote Functional Groups in Acyclic Systems upon Electron Impact[2]

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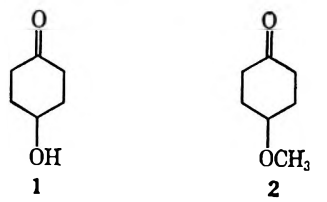
In a series of 4-alkoxybutyrates and related substances, the scope and limitations of the unexpected β cleavage at the ether function have been investigated. Deuterium-labeling experiments and high resolution mass measurements indicated that no rearrangements or reciprocal hydrogen transfers were involved in this process. The intensity of the β-cleavage ion became unimportant as the alkoxy group increased in size. Major fragmentation pathways were elucidated with the aid of high resolution mass measurements, metastable defocusing techniques, and deuterium-labeling studies, and indirect evidence for interaction of the remote functional groups was found.

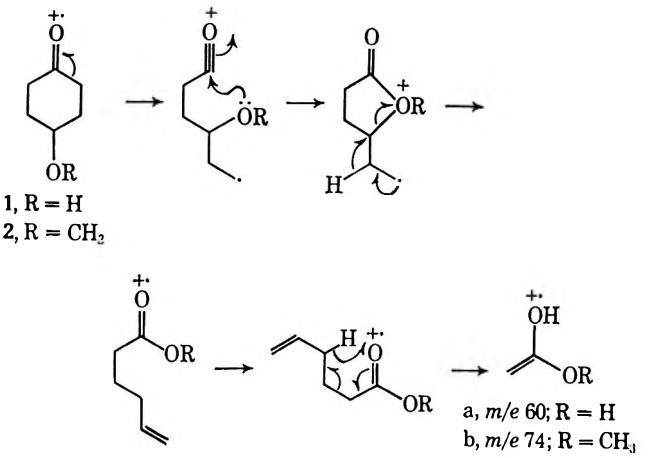
Shortly after the applicability of mass spectrometry to organic chemistry was recognized, the fragmentation patterns of almost every class of compound were extensively investigated, notably with the aid of deuterium labeling and high resolution mass measurements.[4] Recently efforts were initiated in these laboratories[5] to develop programs for computer assisted interpretation of the mass spectra of several classes of compounds. Only acyclic, monofunctional substances have been studied thus far, and a substantial degree of success has been achieved. However, one of the ultimate goals of this program is the computer-aided analysis of the spectra of more complicated molecules. To this end it was important to determine whether two functional groups in the same molecule would give rise to fragmentations independent of one another or to unique fragmentations resulting from direct interaction of the two groups. Of the cases studied thus far,[6-13] the latter possibility seems to be more prevelant. Direct interaction of the functional groups,[6-10] migration of electron rich groups to carbonium ion centers,[11] and anchimeric assistance[12,13] were the reasons cited to explain the unusual fragmentation patterns in these instances.

One of the earliest examples of the interaction of remote functional groups upon electron impact was afforded from studies in our laboratories[6] of the mass spectra of 4-hydroxy- (1) and 4-methoxycyclohexanone (2). Intense ions at m/e 60 for 1 and m/e 74 for 2 were observed, and high resolution mass measurements indicated their composition to be $C_2H_4O_2$ and $C_3H_6O_2$, respectively. With the aid of deuterium-labeling studies, the mechanism in Scheme I was offered to account for

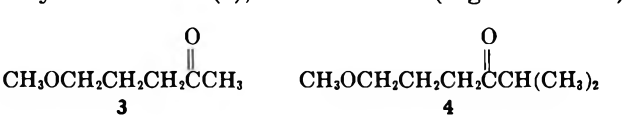


1 2

SCHEME I



the formation of these ions. In the course of that work,[6] the spectra of two acyclic analogs of these substances, 5-methoxy-2-pentanone (3) and 6-methoxy-2-methyl-3-hexanone (4), were recorded (Figure 1 and 2)



3 4

to determine if evidence for interaction of the two functional groups similar to that shown in Scheme I could be found. While no such evidence was encountered in the spectrum of 3, the operation of some functional group interaction in 4 was indicated by the fact that 10% of the intense m/e 59 peak (Figure 2) was shown by high-resolution mass measurements to correspond to

(1) For paper CCI, see S. Eadon, C. Djerassi, J. H. Beynon, and R. M. Caprioli, *Org. Mass. Spectrom.*, submitted for publication.

(2) Financial support from the National Institutes of Health (Grant No. AM 04257) is gratefully acknowledged.

(3) (a) National Science Foundation Postdoctoral Fellow, 1969–1970; (b) National Institutes of Health Postdoctoral Fellow, 1967–1968; (c) Postdoctoral Fellow, 1966–1968.

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(5) (a) J. Lederberg, G. L. Sutherland, B. G. Buchanan, E. A. Feigenbaum, A. V. Robertson, A. M. Duffield, and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 2973 (1969); (b) A. M. Duffield, A. V. Robertson, C. Djerassi, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *ibid.*, **91**, 2977 (1969); (c) G. Schroll, A. M. Duffield, C. Djerassi, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *ibid.*, **91**, 7440 (1969); (d) A. Buchs, A. M. Duffield, G. Schrolli, C. Djerassi, A. B. Delfino, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *ibid.*, **92**, 6871 (1970). (e) Y. M. Sheikh, A. Buchs, A. B. Delfino, G. Schroll, A. M. Duffield, C. Djerassi, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *Org. Mass Spectrom.*, **4**, 493 (1970); (f) A. Buchs, A. B. Delfino, A. M. Duffield, C. Djerassi, B. G. Buchanan, E. A. Feigenbaum, and J. Lederberg, *Helv. Chim. Acta*, **53**, 1394 (1970).

(6) (a) M. M. Green and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 5190 (1967); (b) M. M. Green, D. S. Weinberg, and C. Djerassi, *ibid.*, **88**, 3883 (1966).

(7) M. Vandewalle, N. Schamp, and M. Franque, *Bull. Soc. Chim. Belg.*, **75**, 848 (1966).

(8) R. T. Gray, M. Ikeda, and C. Djerassi, *J. Org. Chem.*, **34**, 4091 (1969).

(9) R. Brandt and C. Djerassi, *Helv. Chim. Acta*, **51**, 1759 (1968).

(10) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **34**, 3147 (1969), and references therein.

(11) (a) R. G. Cooks and D. H. Williams, *Chem. Commun.*, 51 (1967); (b) R. G. Cooks, J. Ronayne, and D. H. Williams, *J. Chem. Soc., C* 2601 (1967).

(12) R. H. Shapiro and K. B. Tomes, *Org. Mass Spectrom.*, **3**, 333 (1970), and references therein.

(13) (a) R. J. Highet and P. F. Highet, *Tetrahedron Lett.*, 1803 (1970); (b) R. E. Wolff and A. Caspar, *ibid.*, 1807 (1970).

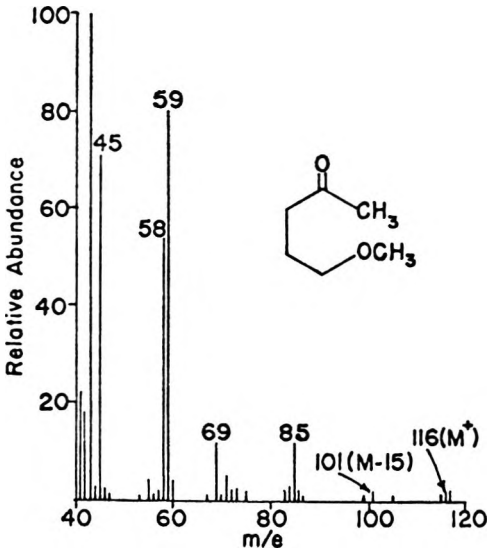
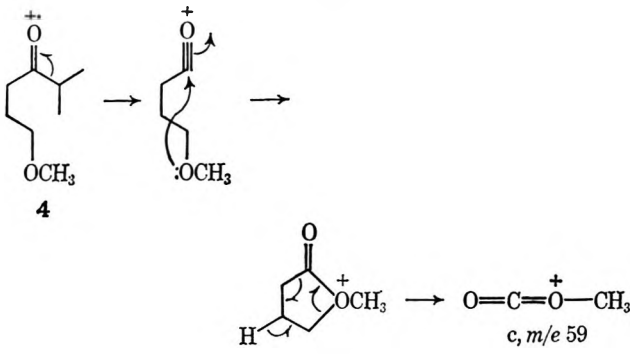


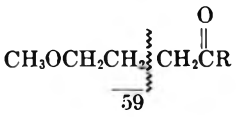
Figure 1.—Mass spectrum (70 eV) of 5-methoxy-2-hexanone (**3**).

$C_2H_3O_2$. Formation of this ion was rationalized as shown in Scheme II. A surprising feature of the spec-

SCHEME II



tra of these two compounds was that the intense (second largest peak at 70 eV, base peak at low electron volts) ions of mass 59 had the composition C_3H_7O (except as mentioned above for **4**), which corresponds formally to β cleavage at the ether function with charge retention on the ether moiety. Under normal circumstances, β cleavage in aliphatic ethers is not a favorable process (methyl butyl ether has only a very small peak at m/e 59).[14,15] Likewise β cleavage at the keto func-



tion with charge retention on the alkyl fragment is also an inefficient process.[16] *A priori*, it would be expected that the favored modes of cleavage in **3** and **4** would be α cleavage at the ether function and a McLafferty rearrangement[17] at the keto function; indeed, intense peaks corresponding to these cleavages were observed in Figures 1 and 2. However, the m/e 59 peak appears to be of equal importance in both cases. Thus it was felt that this anomalous cleavage might be due to some type of interaction of the two functional groups, and,

(14) Reference 4, p 227.
(15) S. L. Bernasek and R. G. Cooks, *Org. Mass Spectrom.*, **3**, 127 (1970).
(16) Reference 4, p 135.
(17) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

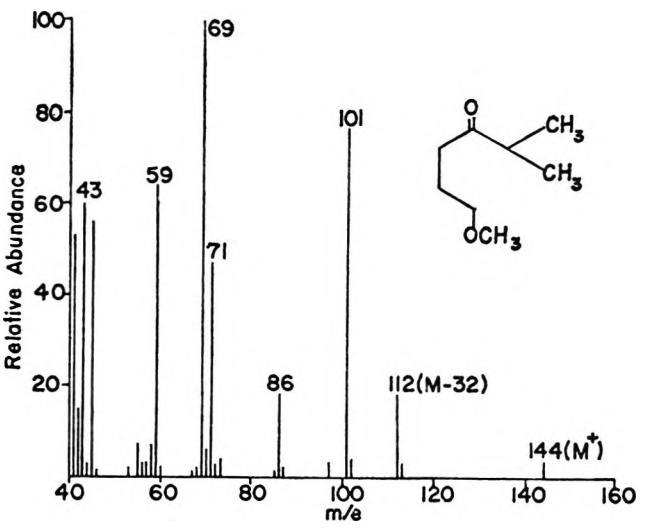


Figure 2.—Mass spectrum (70 eV) of 6-methoxy-2-methyl-3-hexanone (**4**).

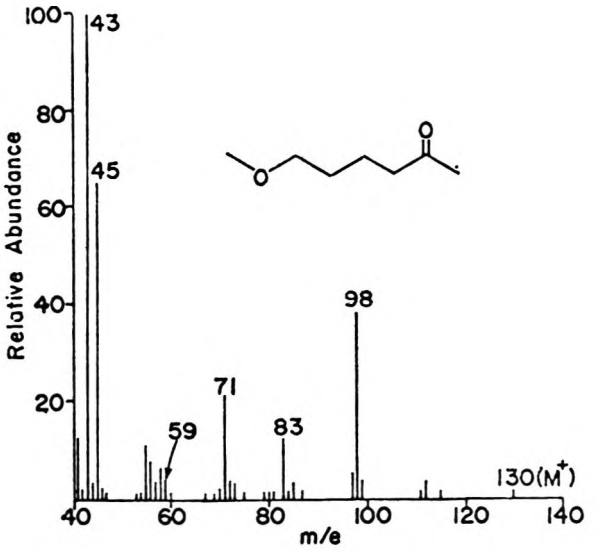
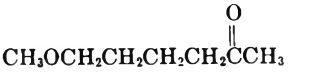


Figure 3.—Mass spectrum (70 eV) of 6-methoxy-2-hexanone (**5**).

since similar cleavages had been observed in recent studies of the fragmentation patterns of ω-amino esters[13b] and long chain aliphatic methoxy esters,[18] it was of obvious interest to study this problem in greater detail.

Results and Discussion

Compounds **3** and **4** both have a keto function separated by three methylene units from a methyl ether function. As a first step in studying the process leading to the "anomalous" m/e 59 peak, it was decided to determine what the effect of varying the distance between these two groups would be. Accordingly, 6-methoxy-2-hexanone (**5**) was synthesized and its mass spectrum recorded[19] (Figure 3). Inspection of Figure 3 reveals



(18) M. Creef, R. E. Wolff, G. H. Dramman, and J. A. McCloskey, *Org. Mass Spectrom.*, **3**, 399 (1970).
(19) Although all mass spectra were recorded at both 70 and 12 eV, only the 70-eV spectra are reproduced.

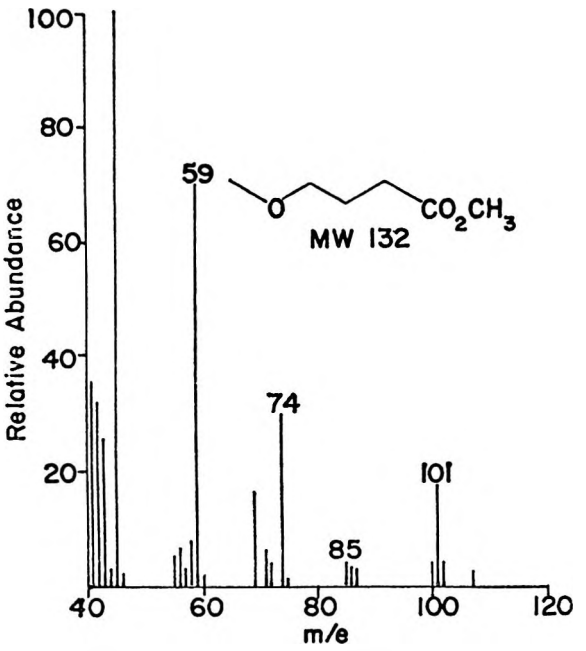


Figure 4.—Mass spectrum (70 eV) of methyl 4-methoxybutyrate (6). No molecular ion was observed in the spectrum.

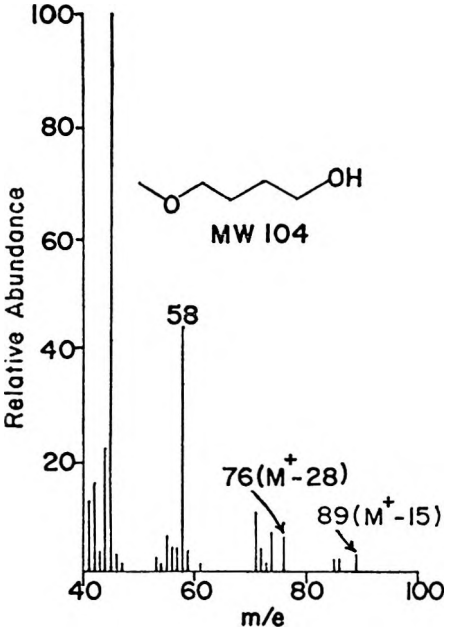


Figure 5.—Mass spectrum (70 eV) of 4-methoxy-1-butanol (7). No molecular ion was observed in the spectrum.

only very low intensity peaks at m/e 59 and 73 (the ion homologous to the ion of mass 59 in the spectrum of **3**), and at low electron volts these peaks disappeared completely. The fragmentation pattern of 4-methoxy-2-butanone was not investigated for the obvious reason that β cleavage at the ether function would also be α cleavage at the keto function in this molecule, a very favorable process.[20] Thus it was concluded that a necessary condition for the formation of the m/e 59 ion in these substances is that the functional groups be separated by three and only three methylene units. This result is in contrast to the situation in the ω-amino esters[13b] where loss of $CH_2CO_2CH_3$ was found to be independent of the separation of the two functional groups.

Having established this condition, it appeared in order to determine if the keto function was also necessary for the formation of this ion. Specifically, would any functional group bearing a carbonyl moiety be sufficient? To this end, methyl 4-methoxybutyrate (**6**) was synthesized and its mass spectrum recorded (Figure 4). As in the spectra of **3** and **4**, the m/e 59

$$\overset{59}{\overbrace{CH_3OCH_2CH_2}}\overset{59}{\overbrace{CH_2CO_2CH_3}} \qquad \text{6}$$

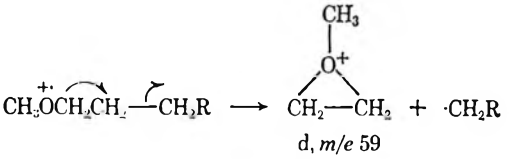
$$CH_3OCH_2CH_2CH_2CO_2H \qquad \text{7}$$

$$CH_3OCH_2CH_2CH_2CH_2CO_2CH_3 \qquad \text{8}$$

fragment in this spectrum was very intense (rel intensity 70%, Σ_{40} 17.5%, base peak at 15 eV). In this instance, α cleavage at the methoxycarbonyl function with charge retention on the methoxycarbonyl group could also give an ion of mass 59. However, high-resolution mass measurements indicated that the composition of this ion was predominately (86%) C_3H_7O; scanning in the metastable mode[21] indicated that the molecular ion was a precursor of this ion. Likewise, in the spectrum (not shown) of 4-methoxybutyric acid (**7**) an intense ion (rel intensity 60%, Σ_{40} 30.0%) of mass 59 was observed. In support of the postulate that the two functional groups could not be separated by more than three methylene units, the spectrum (not shown) of methyl 5-methoxyvalerate (**8**) had no peaks at either m/e 59 or 73. These results led to the conclusion that the keto function could be replaced by other groups bearing a carbonyl moiety to give the m/e 59 peak, and it now remained to be established whether any oxygen-containing function would suffice to produce this ion. The preparation of 4-methoxy-1-butanol (**9**) was therefore effected and its mass spectrum (Figure 5) recorded. Only very small peaks were found at m/e 59

$$CH_3OCH_2CH_2CH_2CH_2OH \qquad \text{9}$$

at both high and low ionizing voltages; instead, a very intense peak appeared at m/e 58, which corresponds to the loss of the elements of water and ethylene from the parent ion (the structure of this ion will be discussed in a forthcoming communication in the context of a related problem). Apparently a carbonyl function is necessary for the formation of the m/e 59 peak. Thus, it was concluded that, in order to generate this anomalous ion from a methyl ether, a carbonyl function has to be located in the molecule and be separated by three methylene units from the ether function. The simplest explanation of these results is that this process is dependent upon the stability of the departing radical, $\cdot CH_2R$, with some driving force being provided by anchimeric assistance from the methoxy group to give the oxiranium ion d. When R = $COCH_3$, CO_2CH_3, or CO_2H, the



radical is allylically stabilized, whereas when R = CH_2-OH or alkyl there is no possibility of such stabilization.

(20) Reference 4, p 134.

(21) (a) J. H. Beynon, *Nature*, **204**, 67 (1964); (b) K. R. Jennings, "Some Newer Physical Methods in Structural Chemistry," R. Bonnett and J. G. Davies, Ed., United Trade Press, London, 1967, p 105.

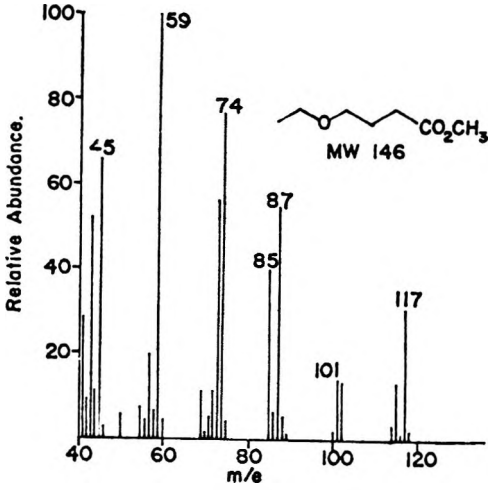


Figure 6.—Mass spectrum (70 eV) of methyl 4-ethoxybutyrate (13). No molecular ion was observed in the spectrum.

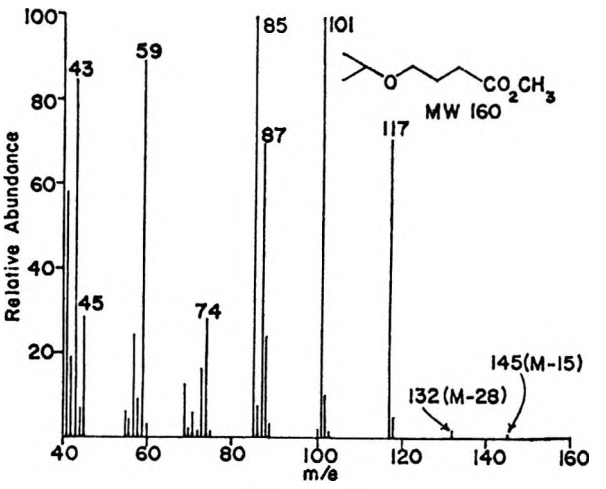


Figure 7.—Mass spectrum (70 eV) of methyl 4-isopropoxybutyrate (14). No molecular ion was observed in the spectrum.

Essentially the same conclusions were reached in the case of the ω-amino esters.[13b]

In order to verify that no hidden rearrangements or reciprocal hydrogen transfer reactions were occurring to give ion d, several deuterated analogs of **6** were synthesized and their mass spectra recorded. Table I lists the

TABLE I

PARTIAL MASS SPECTRAL PEAKS IN THE SPECTRA OF METHYL 4-METHOXYBUTYRATE AND SOME DEUTERATED ANALOGS[a]

m/e	$CH_3O(CH_2)_2CO_2CH_3$	$CH_3OCD_2(CH_2)_2CO_2CH_3$[b]	$CH_3O(CH_2)_2CD_2CO_2CH_3$[c]	$CH_3O(CH_2)_3CO_2CD_3$[d]
59	70	17	79	88
60	2	3	3	4
61		62	1	3
62		1		10

[a] At 70 eV, heated inlet. See also the Experimental Section. [b] 97% d_2, 3% d_1. [c] 19% d_0, 36% d_1, 30% d_2, 13% d_3, 2% d_4. [d] 82% d_3, 18% d_2.

pertinent information regarding the *m/e* 59 ion in the spectra of methyl 4-methoxy-4,4-dideuteriobutyrate (**10**), methyl 4-methoxy-2,2-dideuteriobutyrate (**11**), and methyl-d_3 4-methoxybutyrate (**12**). Accounting

$CH_3OCD_2CH_2CH_2CO_2CH_3$ (**10**)

$CH_3OCH_2CH_2CD_2CO_2CH_3$ (**11**)

$CH_3OCH_2CH_2CH_2CO_2CD_3$ (**12**)

for the fact that 14% of the *m/e* 59 ion in the spectrum of **6** had the composition $C_2H_3O_2$, then it may be seen from Table I that the position of ion d is shifted completely to *m/e* 61 in **10** but is unchanged in **11** and **12**. These results confirm that ion d includes carbon atoms 3 and 4 as well as the methyl ether group and thus lend further support to the mechanism shown above.

Having now established the genesis of the "anomalous" ion of mass 59, it was decided to determine what the effect of different ether alkyl groups would be on the formation and intensity of this ion. Accordingly, compounds **13**, **14**, and **15** were synthesized and their mass

$ROCH_2CH_2CH_2CO_2CH_3$

13, R = C_2H_5
14, R = $CH(CH_3)_2$
15, R = *n*-C_4H_9

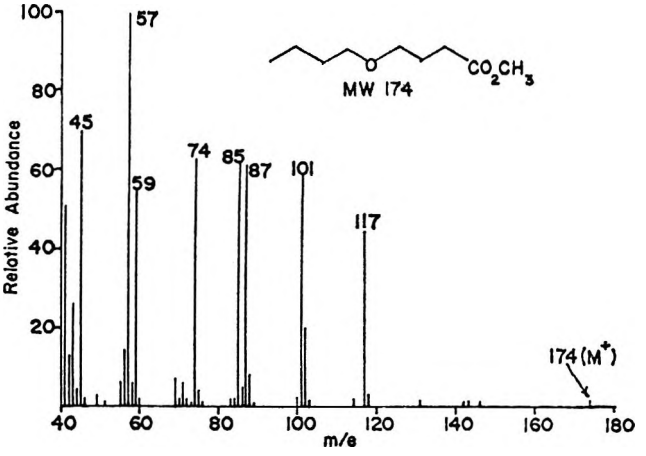


Figure 8.—Mass spectrum (70 eV) of methyl 4-*n*-butoxybutyrate (**15**).

spectra recorded (Figures 6, 7, and 8, respectively). In the spectrum of **13**, the peak analogous to the *m/e* 59 peak in **6** should be shifted by 14 mass units to *m/e* 73 (C_4H_9O), and, as expected, an intense peak was observed at this position (rel intensity 56%, Σ_{40} 8.9%) in Figure 6. However, this ion could also result from β cleavage at the ether function with charge retention on the ester portion of the molecule. This ambiguity was

$C_2H_5OCH_2CH_2\{CH_2CO_2CH_3$

73 73

eliminated by high-resolution mass measurements, which indicated that this ion's composition was C_4H_9O. In addition to coming from the molecular ion, scanning in the metastable mode indicated that the *m/e* 73 fragment (C_4H_9O) also arose from ions of masses 101 ($C_5H_9O_2$) and 115 ($C_6H_{11}O_2$). Fragments analogous to d in **14** and **15** should be shifted to *m/e* 87 and 101, respectively, and Figures 7 and 8 show intense peaks at these

$(CH_3)CHOCH_2\{CH_2\{CH_2CO_2CH_3$ (87)

n-$C_4H_9O\{CH_2CH_2\{CH_2CO_2CH_3$ (101)

TABLE II

PRINCIPAL MASS SPECTRAL PEAKS IN THE SPECTRA OF METHYL 4-ALKOXYBUTYRATES,[a] $RO(CH_2)_3CO_2CH_3$

		m/e values (% relative abundance)								
Compd, R =	No.	M^+	M − R	M − OCH_3	M − OR	$C_4H_7O_2$	M − (R + CH_3OH)	McLafferty ion	$C_3H_2O^b$ + $C_2H_3O_2$	C_2H_4O
CH_3	6	132 (0)	117 (2)	101 (17)	101 (17)	87 (3)	85 (4)	74 (30)	59 (70)	45 (100)
C_2H_5	13	146 (0)	117 (31)	115 (13)	101 (14)	85 (55)	85 (40)	74 (77)	59 (100)	45 (64)
$CH(CH_3)_2$	14	160 (0)	117 (71)	129 (0)	101 (100)	87 (70)[c]	85 (100)	74 (28)	59 (89)	45 (28)
n-C_4H_9	15	174 (0)	117 (100)	143 (2)	101 (54)[d]	87 (62)	85 (56)	74 (87)	59 (55)	45 (70)

[a] Footnote *a*, Table I. [b] For details see Table V. [c] 3% $C_5H_{11}O$. [d] 18% $C_6H_{13}O$.

TABLE III

PRINCIPAL MASS SPECTRAL PEAKS IN THE SPECTRA OF METHYL 4-ETHOXYBUTYRATE AND SOME DEUTERATED ANALOGS[a]

		Approx % of isotopic	m/e values (% relative abundance)								
Compd	No.	purity	M^+	M − Et	M − OCH_3	M − EtO	$C_4H_7O_2$	M − (R + CH_3OH)	McLafferty ion	$C_2H_3O_2$	C_2H_6O
$EtO(CH_2)_3CO_2CH_3$	13		146 (0)	117 (31)	115 (13)	101 (14)	87 (55)	85 (40)	74 (77)	59 (100)	45 (63)
$EtOCD_2(CH_2)_2CO_2CH_3$	16	97 d_2, 3 d_1	148 (0)	119 (28)	117 (13)	103 (15)	89 (50)	86 (30)	75 (33)	59 (29)	45 (19)
										61 (100)	47 (46)
$EtOCH_2(CD_2)_2CO_2CH_3$	17	86 d_4, 14 d_3	150 (0)	121 (42)	119 (20)	105 (24)	91 (62)	89 (53)	76 (100)	59 (97)	45 (71)
										61 (58)	47 (67)
											49 (0)
$EtO(CH_2)_3CO_2CD_3$	18	18 d_2, 83 d_3	149 (0)	120 (37)	115 (20)	104 (20)	87 (61)	85 (60)	77 (87)	59 (100)	45 (29)
										62 (39)	48 (9)

[a] Footnote *a*, Table I.

positions. As in the spectrum of **13**, two different compositions are possible for each ion. In these instances, however, high-resolution mass measurements indicated that the *m/e* 87 peak corresponded predominately (97%) to $C_4H_7O_2$ and the *m/e* 101 peak largely (82%) to $C_5H_9O_2$. *These data indicate that the generation of ions analogous to d (m/e 59) is not favorable in the higher alkoxybutyrates.* It is probable that this is a result of a decrease in the ion current available for the β-cleavage ion because of the increased number of possible modes of fragmentation (note the intense peaks at *m/e* 43 in Figure 7 and *m/e* 55, 57, and 71 in Figure 8) in these substances rather than an increase in the energy requirements for the β-cleavage process.

Dramatic differences between the higher mass regions are noticed when Figure 4 is compared to Figures 6–8. Not only are the intensities of the ions in this region much larger in the latter three spectra, but also ions appear there which are not present in Figure 4. The positions and intensities of some of these ions are summarized in Table II, and the reasons for these differences and probable origin of these ions are discussed below.

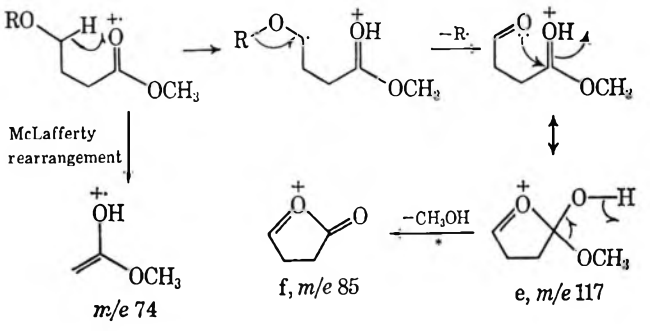
m/e **117 and 85 Peaks.**—Excluding that of **6**, the highest mass peak of major significance in the spectra (Figures 6–8) of the 4-alkoxybutyrates (**13–15**) was found at *m/e* 117. The composition of this ion was found to be $C_5H_9O_2$ in each case, which corresponds to the loss of the alkyl portion of the ether function. Intense metastable peaks were also observed in these spectra in the region *m/e* 61.6–61.8, formally representing the loss of methanol from the *m/e* 117 fragment ($85^2/117$ = 61.7). High-resolution mass measurements for each substance indicated the composition of the mass 85 ion to be $C_4H_5O_2$, and metastable mode scanning experiments[21] likewise indicated that the mass 117 fragment was the only precursor of this ion. To further elucidate the mechanistic details of these transformations, several deuterium-labeled analogs (**16–18**) of **13** were synthesized and their mass spectra recorded. The pertinent spectral data for these substances are summarized in

$C_2H_5OCD_2CH_2CH_2CO_2CH_3$ **16**

$C_2H_5OCH_2CD_2CD_2CO_2CH_3$ **17**

$C_2H_5OCH_2CH_2CH_2CO_2CD_3$ **18**

Table III. It is easily seen from this table that it is the terminal ethyl group that is lost to give the *m/e* 117 ion in **13**. Likewise it can be deduced that the loss of methanol from the *m/e* 117 precursor involves the methoxycarbonyl group and the hydrogen atoms attached to the C-4 carbon atom. A mechanism consistent with these data is shown below. That the *m/e* 117



peak is not present in the spectrum of **6** is probably a reflection of the lower stability of the methyl radical in comparison to the ethyl, isopropyl, and *n*-butyl radicals. Although it is a matter of conjecture whether these ions are best represented by open chain or cyclic structures, it is probable that in view of the conceivable alternatives e and f represent the lowest energy forms. It is interesting that the first step in this process is also the first step in the McLafferty rearrangement, indicating perhaps that in these instances the McLafferty rearrangement is not concerted. However, the overall process does not seem to be competitive with this rearrangement, since the *m/e* 74 ion (McLafferty rearrangement ion) is prominent in the spectra of all of the alkoxybutyrates.

m/e **101 and 102 Peaks.**—Table II shows that in general the intensity of the fragment of mass 101 in

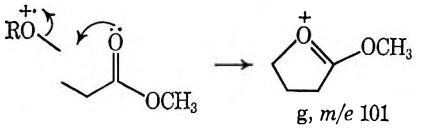
TABLE IV

PRINCIPAL MASS SPECTRAL PEAKS IN THE SPECTRA OF METHYL-d_3 4-ALKOXYBUTYRATES, $RO(CH_2)_3CO_2CD_3$[a]

		Approx % of isotopic	m/e values (% relative abundance)							
Compd, R =	No.	purity	M+	M − R	M − OR	$C_4H_7O_2$	M − (R + CH_3OH)	McLafferty ion	$C_2H_3O_2$	C_2H_3O
CH_3	12	82 d_3, 18 d_2	135 (0)	120 (3)	101 (30) 104 (2)	87 (1)	85 (4)	77 (40)	59 (88) 62 (10)	45 (100) 48 (2)
C_2H_5	18	18 d_2, 82 d_3	149 (0)	120 (37)	101 (0) 104 (20)	87 (61)	85 (60)	77 (87)	59 (100) 62 (40)	45 (79) 48 (9)
$CH(CH_3)_2$	19	21 d_2, 79 d_3	163 (0)	120 (45)	101 (0) 104 (70)	87 (59)[b]	85 (100)	77 (60)	59 (8) 62 (67)	45 (28) 48 (2)
n-C_4H_9	20	19 d_2, 81 d_3	177 (0)	120 (30)	101 (15)[c] 104 (50)	87 (50)	85 (58)	77 (50)	5 (2) 62 (44)	45 (53) 48 (10)

[a] Footnote *a*, Table I. [b] 3% $C_5H_{11}O$. [c] $C_6H_{13}O$.

the spectra (Figures 4, 6–8) of **6, 13, 14,** and **15** increases as the size of the alkyl group increases. For **6**, this fragment can be formed by loss of a methoxy group from either the ether terminus or the methoxycarbonyl group. In general, the latter process does not appear to be very favorable (column 3, Table II). High-resolution mass measurements showed the composition of this ion to be $C_5H_9O_2$ (except for the 18% contribution of $C_4H_{13}O$ in the spectrum of **15**). If the structure of this ion is correctly represented by g, then it would be expected that the position of this peak should be shifted to *m/e* 104 in the spectra of the methyl-d_3 esters. These

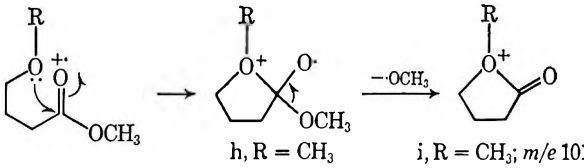


g, *m/e* 101

esters were prepared from the corresponding acids using deuterated diazomethane,[22] and their relevant spectral data are summarized in Table IV. With the exception

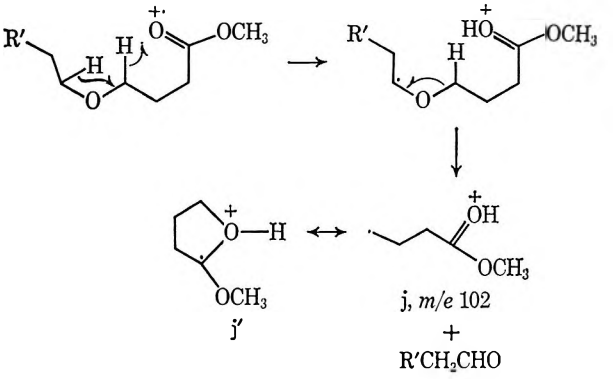
$RO(CH_2)_3CO_2CD_3$
12, R = CH_3
18, R = C_2H_5
19, R = $CH(CH_3)_2$
20, R = n-C_4H_9

of the spectrum of **12**, the fragment of mass 101 was shifted to *m/e* 104 (the small fragment at *m/e* 101 in the spectrum of **20** is due to the β-cleavage ion, $C_6H_{13}O$). The fact that the methoxy group in **12** is lost from the methoxycarbonyl group in contrast to the situation found in the other ethers (**18–20**) is somewhat difficult to rationalize. It was first thought that these results could be explained on the basis of radical stabilities; that is, that the methoxy radical was much less stable than the other alkoxy radicals. However, it has recently been shown[23] that there exists no difference in the stabilities of the methoxy, ethoxy, isopropoxy, and *n*-butoxy radicals. Perhaps the best explanation may be the increased steric hindrance to formation of cyclic intermediates in the larger systems. For R = CH_3, attack of the methoxy oxygen on the ester carbonyl followed by loss of a methoxy radical would give the very stable ion i. For R greater than methyl, however, the increased steric hindrance inhibits the formation of h, and the alkoxy radical is lost from the terminus to give ion g.



h, R = CH_3 i, R = CH_3; *m/e* 101

The composition of the fragment of mass 102 in the spectra of **13**, **14**, and **15** was shown by high-resolution mass measurements to be $C_5H_{10}O_2$, and the position of this peak was shifted to *m/e* 105 in the spectra (Table IV) of **18**, **19**, and **20** and to *m/e* 104 and 106 in the spectra (Table III) of **16** and **17**, respectively. Thus this fragment must contain the methoxycarbonyl group and carbon atoms 2, 3, and 4 as well as a hydrogen atom from the ether alkyl group. Formally this corresponds to an ionized methyl butyrate molecule, although there is no driving force to form this ion. A possible mechanistic pathway leading to the *m/e* 102 fragment is given below. To test the validity of this mechanism, com-



j′ j, *m/e* 102 + $R'CH_2CHO$

pounds **21** and **22** were synthesized and their mass spectra recorded. In the spectrum of **21** (not shown), the characteristic peaks at *m/e* 117, 102, 101, 87, 85, 74, 59, and 45 were exhibited, in addition to a small peak of mass 129 corresponding to β cleavage at the ether function. According to the above formulation, it would be expected that the *m/e* 102 peak in the spectrum of **21**

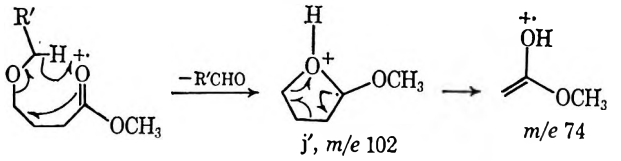
$CH_3(CH_2)_4CH_2O(CH_2)_8CO_2CH_3$ **21** $CH_3(CH_2)_4CD_2O(CH_2)_3CO_2CH_3$ **22**

should be shifted to *m/e* 103 in the spectrum of **22** (not shown), and indeed, accounting for the contribution of the ^{13}C isotope of the *m/e* 101 peak, the *m/e* 102 peak was shifted completely to *m/e* 103 in the spectrum of **22**. An unexpected result encountered in the spectra of

(22) (a) K. J. Van Der Merwe, P. S. Steyn, and S. H. Eggers, *Tetrahedron Lett.*, 3923 (1964); (b) D. W. Thomas and K. Biemann, *J. Amer. Chem. Soc.*, **87**, 5447 (1965).

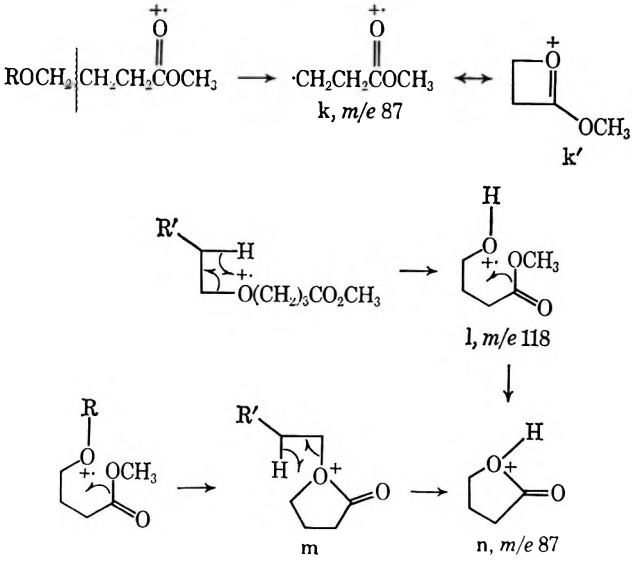
(23) S. W. Benson and R. Shaw, *Advan Chem. Ser.*, **75**, 288 (1969).

these two substances was that the peak of mass 74 in the spectrum of **21** (McLafferty ion) was shifted about 50% to *m/e* 75 in the spectrum of **22**. This result suggests that at least in part the peaks at masses 102 and 74 were not formed as indicated above. A possible alternative formulation is shown below.



j', *m/e* 102 *m/e* 74

m/e **87 Peak.**—Whereas there is only a very weak peak at *m/e* 87 in the spectrum (Figure 4) of **6**, this peak is of major importance in the spectra (Figures 6–8) of the other esters. The composition of this ion was found to be $C_4H_7O_2$ (except in the spectrum of **14**, for which 3% was found to be $C_5H_{11}O$). Some probable structures for this ion and their possible modes of formation are shown below. Of these possible structures (k, k', n), several lines of evidence indicate that n is the best representation of this ion. First, a strong metastable ion was observed at *m/e* 65.8 ($87^2/115 = 65.9$) in the spectrum (Figure 6) of **13**. Second, for **14** and **15** scanning in the metastable mode indicated that the mass 87 ion did not originate from the corresponding molecular ions but rather from a mass 118 precursor as well as from other fragment ions (*m/e* 102 and 129 for **14** and 102 and 143 for **15**). Finally, Tables III and IV show conclusively that the *m/e* 87 fragment contains the C-4 carbon atom but not the ester methoxyl moiety. It is not clear whether n is formed from l or m, and evidence from scanning in the metastable mode indicates that it is probably formed from both. Whether from l or m, it is easy to see why this is not a very favorable process in the spectrum of **6** since the initial transfer of a hydrogen atom from the alkyl chain would not be very feasible.



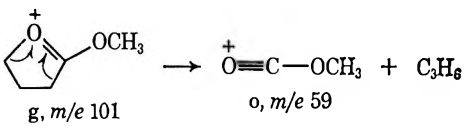
m/e **59 Peak.**—The composition of this ion was found to be a mixture of C_3H_7O and $C_2H_3O_2$, and Table V lists the percentages of the two compositions for each of the alkoxybutyrates. Also listed there are the results of some metastable mode scanning experiments carried out on this ion. Because of the complexity of the data associated with this ion, few general conclusions can be drawn regarding its genesis. As mentioned earlier, the major portion of the *m/e* 59 peak in the spectrum of **6** is attributable to the β-cleavage ion d; presumably the minor component is derived by α cleavage at the carbomethoxy function to give o.

TABLE V

SUMMARY OF THE HIGH RESOLUTION AND METASTABLE DEFOCUSING DATA FOR THE *m/e* 59 PEAK IN THE SPECTRA OF THE METHYL 4-ALKOXYBUTYRATES, $RO(CH_2)_3CO_2CH_3$

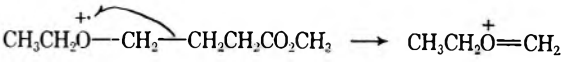
Compd, R =	No.	C_3H_7O, %	$C_2H_3O_2$, %	Probable parent ions[a]
CH_3	6	86	14	87, 101, 132
C_2H_5	13	78	22	87, 101
$CH(CH_3)_2$	14	66	34	87, 101
n-C_4H_9	15	35	65	85, 87, 101, 116

[a] As determined by the metastable defocusing technique.



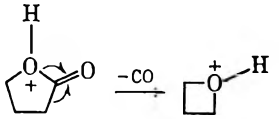
g, *m/e* 101 o, *m/e* 59

In the case of **13**, α cleavage at the ether function would give p with the composition C_3H_7O. Table III lends support to this hypothesis in that in the spectrum



14 p, *m/e* 59

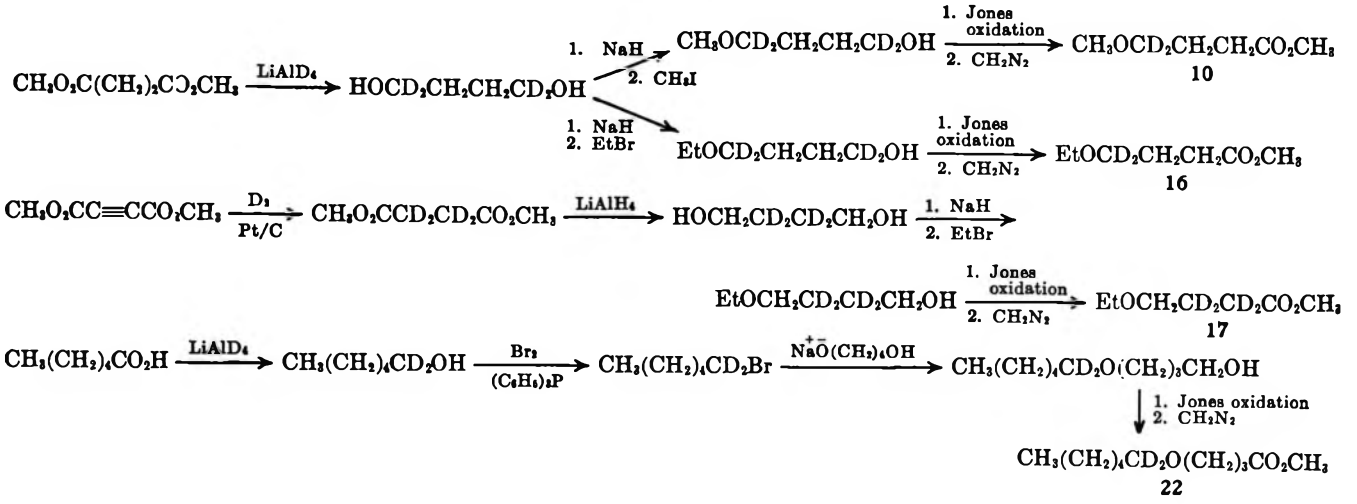
of **16** a large portion of the *m/e* 59 peak is shifted to *m/e* 61. Again it is probable that to a large extent the minor component of this ion is formed by α cleavage at the carbomethoxy function to give o. The metastable mode scanning results listed in Table V indicate that in all four esters this ion is formed to some extent from an *m/e* 87 precursor. Assuming the structure of the *m/e* 87 ion to be as postulated above (n), then *m/e* 59 can be formed by loss of carbon monoxide from n to give q.



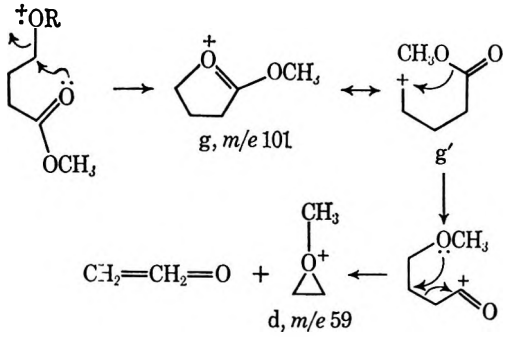
n, *m/e* 87 q, *m/e* 59

In the spectrum of **14**, the formation of the C_3H_7O portion of the mass 59 ion is more difficult to rationalize. Whereas the major portion of this ion was shown to have the composition C_3H_7O, its position was shifted almost entirely to *m/e* 62 in the spectrum (Table IV) of **19**. These results imply either that the predominant composition of this ion is $C_2H_3O_2$ or that some unusual rearrangement of the methoxy moiety to the alkyl chain is occurring. Similar puzzling results exist for **15** in that high-resolution mass measurements indicate the ratio of the abundances of the C_3H_7O to $C_2H_3O_2$ ions to be roughly 1:2, whereas the spectrum (Table IV) of **20** indicates this ratio to be on the order of 1:20. These apparent inconsistencies were clarified by high-resolution mass measurements of the *m/e* 62 fragment in the spectra of **19** and **20**. These measurements indicated that $C_3H_4D_3O$ and not $C_2D_3O_2$ was the predominant composition of this fragment (relative intensities of 65:35% in **19** and 61:39% in **20**, respectively). Thus,

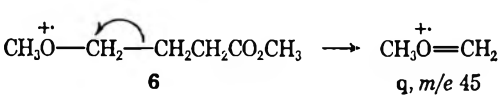
SCHEME III



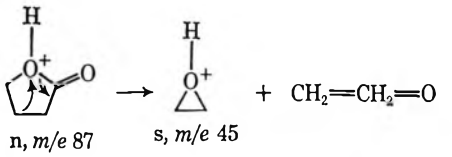
contrary to expectations, migration of the methoxy group from the carbonyl group to an sp^3 hybridized carbon atom must have occurred. Bearing in mind that the *m/e* 101 fragment was a precursor of the *m/e* 59 fragment common to all four unlabeled esters (**6**, **13**, **14**, and **15**), a possible formulation of the genesis of the *m/e* 59 fragment of composition C_3H_7O in the spectra (Figures 7 and 8) of **14** and **15** is given below. Migrations of methoxyl groups to carbonium ion centers have been shown previously[11] to be facile processes.



m/e **45 Peak.**—A substantial peak was exhibited at *m/e* 45 in the spectra of all four alkoxy esters. The only composition allowable for this ion is C_2H_5O. In the spectrum of **6** this ion is the base peak and undoubtedly results from the usual α cleavage at the ether function to give q.[24] This conclusion is supported by the findings that the position of this ion is shifted to

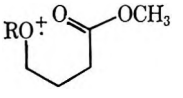


m/e 47 in the spectrum of **10** but is unchanged in the spectra of **11** and **12**. For **13**, **14**, and **15** there appears to be a variety of possible ways to form C_2H_5O. Indeed, the data in Tables III and IV and the results from metastable defocusing experiments indicate that such is the case. Considering, for instance, the *n*-butoxy ether **15**, ions of mass 73, 87, 101, and 132 were indicated as probable precursors for the *m/e* 45 ion. Likewise, for the ethoxy derivative **13** it was shown that the two carbon atoms in this fragment came partially from C-3, C-4, and the ethyl group. The only ion common to all four esters implicated as a possible precursor of the *m/e* 45 ion was the *m/e* 87 ion.



(24) The exact structure of the α-cleavage ions of aliphatic ethers has recently been studied in detail by ion spectroscopy. See J. Beauchamp and R. C. Dumbar, *J. Amer. Chem. Soc.*, **92**, 1477 (1970).

Summary.—One of the purposes of this work was to investigate whether the ion of mass 59 in the spectra of **3** and **4** resulted from an interaction of the two functional groups. In general, no evidence could be found linking the direct interaction of the two groups with the formation of this ion. However, indirect evidence for such interactions in the spectra of the alkoxybutyrates was deduced from an analysis of the *m/e* 117, 101, and 85 peaks. Several fragmentations were also noted which were characteristic of the individual functional groups. It is probable that the functional group interactions were facilitated by charge sharing between the two functional groups to give a coiled molecular ion.[9]



Syntheses of Labeled Compounds.—For this investigation it was necessary to synthesize several labeled 4-alkoxybutyrates with deuterium at the C-2, C-3, and C-4 positions as well as at the carbon in the alkyl chain α to the ether oxygen. The reaction pathways employed to obtain these substances are summarized in Scheme III, and the isotopic purity of the products is given in the appropriate table.

Experimental Section

The low-resolution mass spectra were obtained by Mr. R. G. Ross using an AEI MS-9 double-focusing mass spectrometer (heated inlet 150°, ion source temperature 180°). The high-resolution data were also obtained by Mr. Ross with the same instrument, and metastable transitions in the first-field-free region were observed with the aid of the metastable defocusing

technique.[21] All substances were purified by vpc (5 ft × 0.25 in. SE-30, 5%, on Chromosorb G), prior to spectral analyses.

Infrared spectral data were recorded with a Perkin-Elmer Model 700 spectrophotometer, and the nmr spectra were secured with a Varian Model T-60 spectrometer. All nmr measurements were made in CCl_4 solutions containing 1% TMS as an internal standard. Chemical shifts are reported in parts per million downfield from the standard, and coupling constants are reported in hertz. Elemental analyses were performed by Mr. E. Meier and Mr. J. Consul of the Stanford Microanalytical Laboratory.

Methyl 4-Alkoxybutyrates.—The substances were prepared by Jones oxidation[25] of the corresponding 4-alkoxy-1-butanol to the acid and subsequent methylation of the acid with diazomethane. In a typical procedure a 1:10 solution of the appropriate 4-alkoxy-1-butanol in acetone (distilled from $KMnO_4$) was cooled to 0° and Jones reagent[26] was added dropwise with stirring until the color of the reagent persisted. The reaction mixture was then stirred at room temperature for 30 min and the chromium salts were filtered off. Acetone was removed at reduced pressure, excess saturated NaCl solution added, and the solution extracted three times with ether. The ether solution was dried ($MgSO_4$) and concentrated, and the acid was then esterified with diazomethane in the usual manner[27] without further purification. The methyl 4-alkoxybutyrates were separated from the crude reaction mixtures by distillation at reduced pressures and vpc and were identified by their ir, nmr, and mass spectra.

Methyl 4-methoxybutyrate (**6**): bp 60–62° (8 mm) [lit.[28] bp 70–71° (11 mm)]; ir (film) 1735 cm^{-1} (C=O); nmr δ 3.60 (s, 3 H, CO_2CH_3), 3.33 (t, 2 H, J = 6 Hz, CH_2O), 3.26 (s, 3 H, CH_3O), 2.32 (m, 2 H, CH_2CO_2), 1.85 (m, 2 H, CH_2CH_2O).

Methyl 4-ethoxybutyrate (**13**): bp 68° (7 mm); ir (CCl_4) 1740 cm^{-1} (C=O); nmr δ 3.63 (s, 3 H, CO_2CH_3), 3.38 (m, 4 H, CH_2O), 2.34 (t, 2 H, J = 6 Hz, CH_2CO_2), 1.82 (m, 2 H, CH_2CH_2O), 1.13 (t, 3 H, J = 6 Hz, CH_3CH_2). *Anal.* Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.47; H, 9.38.

Methyl 4-isopropoxybutyrate (**14**): bp 66–70° (5 mm); ir (CCl_4) 1740 cm^{-1} (C=O); nmr δ 3.60 (s, 3 H, CO_2CH_3), 3.37 (m, 3 H, CH_2O, CHO), 2.34 (t, J = 6 Hz, CH_2CO_2), 1.84 (m, 2 H, CH_2CH_2O), 1.07 (d, 6 H, J = 6 Hz, $(CH_3)_2CH$). *Anal.* Calcd for $C_8H_{16}O_3$: C, 60.00; H, 10.10. Found: C, 59.82, H, 9.95.

Methyl 4-*n*-butoxybutyrate (**15**): bp 73–75° (4 mm); ir (film) 1738 cm^{-1} (C=O); nmr δ 3.62 (s, 3 H, CO_2CH_3), 3.35 (t, 4 H, J = 6 Hz, CH_2OCH_2), 2.30 (t, 2 H, J = 6 Hz, CH_2CO_2), 1.89 (m, 2 H, $CH_2CH_2CO_2$), 1.41 (m, 4 H, CH_2CH_2), 0.87 (m, 3 H, CH_3CH_2). *Anal.* Calcd for $C_9H_{18}O_3$: C, 62.01; H, 10.41. Found: C, 61.78; H, 10.20.

Methyl 4-*n*-hexoxybutyrate (**21**): bp 88° (2 mm); ir (film) 1740 cm^{-1} (C=O); nmr δ 3.64 (s, 3 H, CO_2CH_3), 3.37 (m, 4 H, CH_2O), 2.30 (m, 2 H, CH_2CO_2), 1.27 (m, 10 H, CH_2CH_2), 0.87 (m, 3 H, CH_3CH_2). *Anal.* Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.42; H, 10.91.

6-Methoxy-2-hexanone (**5**).—Methylation of 5-carboxyl-2-pentanone (Aldrich Chemical Co.) with diazomethane was carried out in the usual manner to give 5-methoxycarbonyl-2-pentanone. To 4.5 g of this ester in 50 ml of benzene was added 2.1 g of ethylene glycol and a trace of *p*-toluenesulfonic acid and the mixture was heated overnight. The mixture was cooled, washed with water, dried ($MgSO_4$), and evaporated to give 5.2 g of crude ketal. To 0.8 g of $LiAlH_4$ in 25 ml of ether was added 3.8 g of this ketal and the resultant mixture was stirred for 4 hr at room temperature. Standard work-up yielded 3.4 g of the crude ethylene ketal of 6-hydroxy-2-hexanone. Treatment of 2.4 g of this material with 1.8 g of NaH (54.7% mineral oil dispersion) and 5.5 g of methyl iodide in refluxing benzene for 12 hr yielded the ethylene ketal of the crude 6-methoxy-2-hexanone. Deketalization was accomplished by heating the ketal in 90% aqueous acetic acid for 2 hr. After work-up, the crude product was purified by vpc to give **5**, ir (film) 1708 cm^{-1} (C=O), bp 72° (10 mm) [lit.[29] bp 65–67° (8 mm)].

Methyl 5-Methoxypentanoate (**8**).—To 8.0 g of 1,5-pentanediol mixed with a few milliliters of dry benzene was added slowly 3.8 g of NaH (54.7% mineral oil dispersion) and the resultant mixture was stirred at reflux for 2 hr. After cooling, 34.0 g of methyl iodide was added and refluxing continued for 12 hr. After cooling again, excess saturated NaCl solution was added, the solution was extracted with ether, and the organic extracts were dried ($MgSO_4$) and evaporated to give 4.5 g of yellow oil. Distillation of this material at 80° (7 mm) gave 2.0 g of 5-methoxy-1-pentanol. Conversion of this material to **8** was accomplished by a procedure analogous to that described above for the 4-alkoxybutyrates, bp 70° (9 mm) [lit.[28] bp 70–71° (11 mm)].

Deuterium-Labeled Esters and Alcohols.—The methyl-d_3 4-alkoxybutyrates (**12**, **18**, **19**, and **20**) were prepared from the corresponding 4-alkoxybutyric acids according to the procedure of Biemann,[22b] with the exception that phenol was used instead of phenol-*O*-*d*. The 4,4-dideuterio-4-alkoxybutyrates (**10** and **16**) were prepared from 1,1,4,4-tetradeuterio-1,4-butanediol in the same manner as the unlabeled esters. This tetradeuterated butanediol was obtained by slowly adding 8.7 g of methyl succinate to 3.0 g of $LiAlD_4$ in 150 ml of THF (distilled from $LiAlH_4$), refluxing for 24 hr, and working up in the usual manner. Likewise, methyl 2,2,3,3-tetradeuterio-4-methoxybutyrate (**17**) was prepared from 2,2,3,3-tetradeuterio-1,4-butanediol, and this diol was prepared by catalytic deuteration of methyl acetylenedicarboxylate using deuterium gas (3 atm) and a platinum catalyst (5% on charcoal). Methyl 4-(1′,1′-dideuterio-*n*-hexoxy)butyrate was prepared from 1,1-dideuteriohexyl bromide and 1,4-butanediol in the usual manner. The 1,1-dideuteriohexyl bromide was prepared by an $LiAlD_4$ reduction of hexanoic acid to give 1,1-dideuterio-1-hexanol, followed by bromination of this alcohol using triphenylphosphine and bromine.[30]

Registry No.—**3**, 17429-04-8; **4**, 17429-05-9; **5**, 29006-00-6; **6**, 29006-01-7; **7**, 29006-02-8; **12**, 29006-03-9; **13**, 29006-04-0; **14**, 29006-05-1; **15**, 29006-06-2; **16**, 29006-07-3; **17**, 29006-08-4; **18**, 29006-09-5; **19**, 29006-10-8; **20**, 28995-64-4; **21**, 28995-65-5.

Acknowledgment.—We wish to thank Professor J. I. Brauman for his valuable comments and Professor A. L. Weinheimer (University of Oklahoma) for the preparation of **15** during his sabbatical leave at Stanford University.

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

(26) For preparation of this reagent, see C. Djerassi, R. A. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(27) de Boer and Backer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 250.

(28) S. Hauptman, F. Brandes, E. Bauer, and W. Gabler, *J. Prakt. Chem.*, **25**, 56 (1964).

(29) R. C. Elderfield, B. M. Pitt, and I. Wempen, *J. Amer. Chem. Soc.*, **72**, 1334 (1950).

(30) G. A. Wiley, *et al.*, *ibid.*, **86**, 964 (1964).

Isolation and Identification of the Cis–Trans Stereoisomers of Substituted 3-Hydroxy- (or 3-Acetoxy-) 2-methyl-2,3-dihydrobenzofurans. Dihydrobenzofurans Which Obey the Karplus Equation[1]

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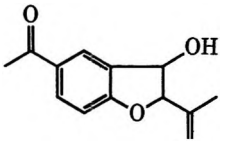
The cis–trans stereoisomers of 5-nitro- and 7-nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofurans (4a–d) were separated by a combination of column chromatography and fractional crystallization. *cis*-7-Nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofuran (4c) was converted to the dimethylamino isomer 5 by catalytic reduction of the nitro group in methanol–formaldehyde. Hydrolysis of the acetyl and quaternization of the amino alcohol 6 gave *cis*-7-dimethylamino-3-hydroxy-2-methyl-2,3-dihydrobenzofuran methiodide (7). The stereoisomers of 4 having $J_{2,3}$ = 2 Hz were assigned trans stereochemistry and the stereoisomers having $J_{2,3}$ = 6 Hz were assigned cis stereochemistry. These assignments were confirmed by determining the X-ray diffraction patterns of the *cis*-MeI salt 7. The X-ray diffraction results confirm the validity of the Karplus equation in predicting the stereochemistry of these substituted 2,3-dihydrobenzofurans.

Recently, Zalkow and Ghosal[2,3] observed that 1,2-trans coupling was greater than cis coupling in the nmr spectra of 2-isopropyl-3-hydroxy- (or acetoxy-) dihydrobenzofurans ($J_{trans\text{-}2,3} > J_{cis\text{-}2,3}$). The failure of the Karplus equation in these systems was attributed to the stereochemical dependence of the electronegativity effect in the cis series. It was proposed that $J_{cis\text{-}2,3}$ is lowered due to a steric interaction of the 2-isopropyl and 3-hydroxy substituents of dihydrotoxol (2). As the C-2 and C-3 substituents bend away from each other, the angle between the 3-hydroxy and C-2 proton approaches 180°, the angle of maximum electronegativity effect and minimum $J_{2,3}$.[4] The authors



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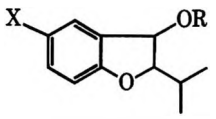
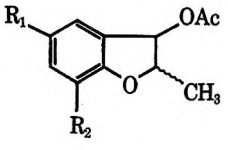


2, X = Ac; R = H
3, X = Br; R = Ac

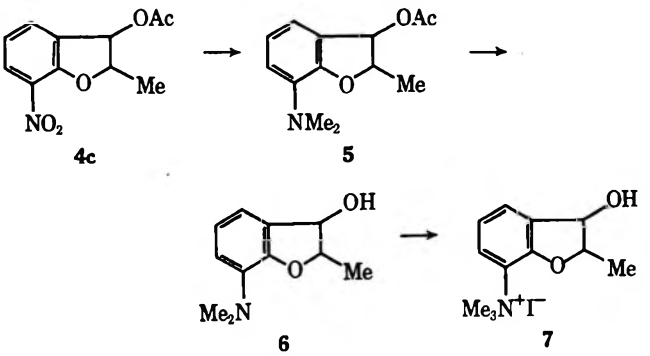


4a (*cis*), $R_1 = NO_2$; $R_2 = H$
b (*trans*), $R_1 = NO_2$; $R_2 = H$
c (*cis*), $R_1 = H$; $R_2 = NO_2$
d (*trans*), $R_1 = H$; $R_2 = NO_2$

conclude that the assignment of stereochemistry based solely on the size of the coupling constants can be misleading in systems such as 2,3-dihydrobenzofurans.

Hayward and coworkers[5] have assigned the stereochemistry of 2,3-dialkyldihydrobenzofurans on the basis of mode of synthesis. The relative magnitude of the coupling constants in this series, $J_{cis\text{-}2,3} > J_{trans\text{-}2,3}$, was as predicted by the Karplus equation and, as the authors note, is not comparable to the models of Zalkow and coworkers since the 3 substituent, being alkyl, would not be expected to have the same "electronegativity effect" as the 3 oxygen.

We wish to report the results of studies on the assignment of cis–trans stereochemistry in 5- and 7-substituted 3-acetoxy- (or hydroxy-) 2-methyldihydrobenzofurans, models similar to those reported in the work of Zalkow and coworkers. The reaction conditions used to synthesize the 2-methyl-2,3-dihydrobenzofurans (4) were similar to those reported[3] in the stereospecific synthesis of 2 and 3. However, the product obtained in the 2-methyl series was a mixture of equal amounts of the cis and trans isomers.[6] The separation of the cis and trans isomers of 4 was accomplished by a combination of column chromatography and fractional crystallization. Each series contained one isomer with $J_{2,3}$ = 2 Hz and one isomer with $J_{2,3}$ = 6 Hz. The initial assignments, assuming the validity of the Karplus equation for series 4, should give the 2,3-cis isomer for $J_{2,3}$ = 6 Hz (4a and 4c) and the 2,3-trans isomer for $J_{2,3}$ = 2 Hz (4b and 4d). However, from the exceptions of Zalkow and Ghosal[2,3] this assumption is subject to question.



4c 5 6 7

(1) Supported by an NDEA Title IV Predoctoral Fellowship, 1966–1969, to L. J. P. and by Grant 1K3-CA-10739 from the National Cancer Institutes, National Institutes of Health. Abstracted from the doctoral dissertation submitted by L. J. P. to the Graduate School, University of Kansas. Support for the X-ray diffraction data system is acknowledged from Grant CA-10104 of the National Institutes of Health. A preliminary communication has been published: M. P. Mertes, L. J. Powers, and E. Shefter, *Chem. Commun.*, 620 (1970).

(2) L. H. Zalkow and M. Ghosal, *ibid.*, 922 (1967).

(3) L. H. Zalkow and M. Ghosal, *J. Org. Chem.*, **34**, 1646 (1969).

(4) H. Booth, *Tetrahedron Lett.*, 411 (1965).

(5) (a) E. C. Hayward, D. S. Tarbell, and L. D. Colebrook, *J. Org. Chem.*, **33**, 399 (1968); (b) K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 516 (1963).

(6) L. J. Powers and M. P. Mertes, *J. Med. Chem.*, **14**, 361 (1971).

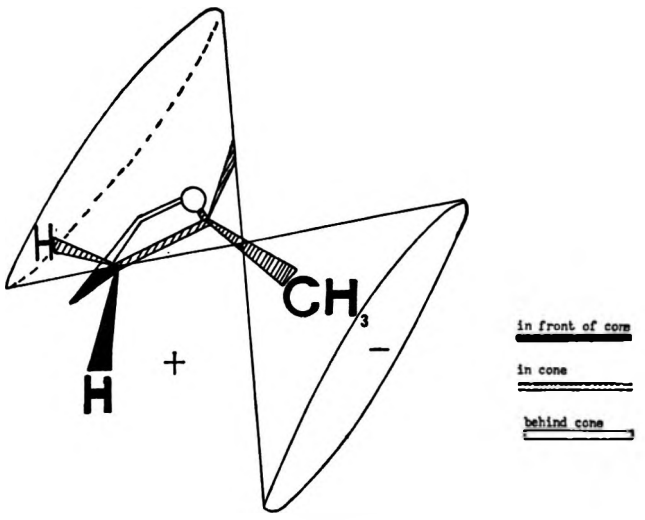


Figure 1.—The anisotropic shielding (+) of the cis C-3 proton and the anisotropic deshielding (−) of the trans C-3 proton by the methyl–C-2 bond in 2-methyl-2,3-dihydrobenzofurans.

Factors that can be considered for structural assignment are the relative magnitude of the coupling constants and the expected changes that would occur in comparing the 2-methyl series (**4**) with the 2-isopropyl series (**2** and **3**). If, as Zalkow and Ghosal[2,3] suggest, the lowering of the coupling constant in the cis series (**2** and **3**) is due to a steric interaction of the C-2 and C-3 substituents, it would seem logical that **3**, having the bulkier 2-isopropyl substituent, would have a greater steric interaction between the C-2 and C-3 substituents, a greater dihedral angle, and hence a lower coupling constant than **4a** and **4c**. In addition, the electronegativity effect exaggerated by an antiplanar orientation would diminish the expected coupling constant.[5b] Thus, these factors must operate to give a value of $J_{cis\text{-}2,3}$ of 3.5 Hz for **2** and **3**, a rather strong effect when compared to a $J_{cis\text{-}2,3}$ of 6 Hz for series **4**.

The reported trans coupling constants for **2** and **3** are 5–6 Hz, high values considering ring distortion should be minimal and the dihedral angle should approach 120°;[5b] the respective trans coupling of 2 Hz is noted in series **4**.

The most striking differences between the nmr spectra of the cis and trans isomers of **4**, other than the values of $J_{2,3}$, are the different values for the chemical shift of the C-3 proton. The C-3 proton of the trans isomers (**4b** and **4d**) is about δ 0.3 upfield from the corresponding C-3 protons of the cis isomers (**4a** and **4c**). This difference in chemical shift was examined by varying temperature nmr studies for a steric interaction of the 2-methyl group and the 3-acetoxy group of the cis isomer which might restrict the free rotation of the acetoxy substituent. No change in the chemical shift of the C-3 proton in the cis series (**4a** and **4c**) was observed in the range −27 to 100°. Since this difference in chemical shift is apparently not a conformational effect, a reasonable explanation is that the difference is due to the proximity of the methyl group to the C-3 proton in the trans stereoisomer (in which the C-2 methyl group and C-3 proton are cis). The basis of such a shielding interaction is the known anisotropic effect of the C–C single bond.[7] As shown in Figure 1, the C-3 proton in the trans stereoisomer of the 2-methyl-3-acetoxy-2,3-dehydrobenzofurans is in a shielding region while the C-3 proton of the cis stereoisomer is in a deshielding region.

(7) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 117.

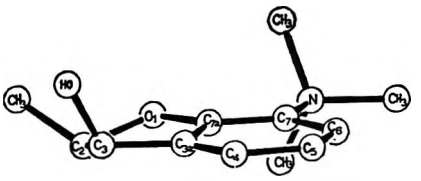


Figure 2.—X-Ray crystal structure of *cis*-7-trimethylammonium 3-hydroxy-2-methyl-2,3-dihydrobenzofuran iodide (**7**).

The mass spectra of the series **4** contain some interesting relationships. The greatest difference between the mass spectra of the cis isomers (**4a** and **4c**) and those of the trans isomers (**4b** and **4d**) is in the relative abundances of the peaks at *m/e* 177 and 178 (loss of CH_3COOH and CH_3COO, respectively) as well as the peaks at *m/e* 131 and 132 (loss of NO_2 and CH_3COOH or CH_3COO). It appears that the trans isomers **4b** and **4d** ($J_{2,3}$ = 2 Hz) have a greater tendency to lose a AcOH fragment relative to the loss of a AcO fragment than do the cis isomers **4a** and **4c** (Table I). This can be explained by assuming that the trans isomers would be in a favorable configuration to undergo a McLafferty[8] rearrangement with the abstraction of the C-2 proton. In the case of the cis isomers **4a** and **4c**, the abstraction would seem to be less favorable as the proton is located on the side of the ring opposite the acetoxy group.

TABLE I

THE RELATIVE PROBABILITY OF THE LOSS OF A CH_3COOH AND CH_3COO FRAGMENT IN THE $J_{2,3}$ = 2 Hz AND $J_{2,3}$ = 6 Hz ISOMERS OF 5-NITRO-3-ACETOXY-2-METHYL-2,3-DIHYDROBENZOFURAN AND 7-NITRO-3-ACETOXY-2-METHYL-2,3-DIHYDROBENZOFURAN

	$J_{2,3}$ = 2 Hz		$J_{2,3}$ = 6 Hz	
	4b	**4d**	**4a**	**4c**
$\frac{m/e\ 177}{m/e\ 178}$	5.1	7.6	3.6	3.9
$\frac{m/e\ 131}{m/e\ 132}$	1.7	1.3	1.1	0.8

In order to prepare a derivative for X-ray crystallographic confirmation of the assigned stereochemistry, the cis nitro acetate **4c** was converted to the methiodide salt **7** and the X-ray diffraction pattern of this salt was determined. The nitro acetate **4c** was converted to the Me_2N analog **5** by a modification of the reductive alkylation procedure of Martell and Boothe.[9] Alkaline hydrolysis of **5** gave *cis*-5-dimethylamino-3-hydroxy-2-methyldihydrobenzofuran (**6**). Conversion of **6** to the methiodide **7** was accomplished in the usual manner. The nmr spectra of the intermediates showed the usual pattern with regard to the C_2 and C_3 protons ($J_{cis\text{-}2,3}$ = 6 Hz).

X-Ray diffraction analysis of compound **7** confirmed cis stereochemistry (Figure 2). The torsion angle, about the 2,3 positions as obtained from the crystal

(8) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1966, Chapter 8.

(9) M. J. Martell, Jr., and J. H. Boothe, *J. Med. Chem.*, **10**, 44 (1967).

structure determination, is shown in Figure 3. Though the hydrogens were not located in this analysis, a 19° angle is a reasonable approximation for their spatial distribution.

The results of this research and that of Hayward and coworkers[5] indicate that in the absence of steric crowding the stereochemistry of 2,3-dihydrobenzofuran systems can be assigned on the assumption that $J_{cis\text{-}2,3} > J_{trans\text{-}2,3}$.

Experimental Section[10]

Isolation and Purification of the Stereoisomers of 5-Nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofuran (4a and 4b) and 7-Nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofuran (4c and 4d).—The crude reaction mixture from the nitration of 3-acetoxy-2-methyl-2,3-dihydrobenzofuran[6] (mixture of stereoisomers) with nitric acid in acetic anhydride was chromatographed as previously described.[6] Three major fractions collected from the silica column contained the nitro acetates **4**. Evaporation of the solvent from the first fraction gave the pure *trans*-5-nitro acetate **4b** as a yellow oil in 13% yield bp 138° (0.2 mm); ir (CCl_4) 1740 (C=O), 1520 and 1355 (NO_2); nmr ($CDCl_3$) δ 1.46 (d, 3, J = 6 Hz, $CHCH_3$), 2.12 (s, 3, $OCOCH_3$), 4.97 (octet, 1, J = 2 and 6 Hz, $CHCH_3$), 5.94 (d, 1, J = 2 Hz, CHOAc), 7.0 (m, 1, aromatic H-7), 8.3 (m, 2, aromatic H-4 and H-6).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.72; H, 4.59; N, 5.94.

The second fraction contained (in 32% yield) a mixture of the *cis*- and *trans*-5-nitro isomers. Crystallization from MeOH followed by recrystallization from C_6H_{12} gave the pure *cis*-5-nitro acetate **4a**: mp 95–97°; ir (KBr) 1736 (C=O), 1508 and 1340 (NO_2); nmr ($CDCl_3$) δ 1.52 (d, 3, J = 6 Hz, $CHCH_3$), 2.10 (s, 3, $OCOCH_3$), 4.95 (quintet, 1, J = 6 Hz, $CHCH_3$), 6.25 (d, 1, J = 6 Hz, CHOAc), 6.90 (d, 1, J = 9 Hz, aromatic H-7), 8.25 (m, 2, aromatic H-4 and H-6).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.59; H, 4.87; N, 5.98.

The third fraction contained a mixture (in 35% yield) of the *cis*- and *trans*-7-nitro acetates. Crystallization from CCl_4 gave the pure *cis*-7-nitro acetate **4c**: mp 129.5–130.5°; ir (KBr) 1732 (C=O), 1525 and 1345 (NO_2); nmr ($CDCl_3$) δ 1.62 (d, 3, J = 6 Hz, $CHCH_3$), 2.10 (s, 3, $OCOCH_3$), 5.03 (quintet, 1, J = 6 Hz, $CHCH_3$), 6.27 (d, 1, J = 6 Hz, CHOAc), 7.05 (t, 1, J = 8 Hz, aromatic H-5), 7.74 (m, 1, aromatic H-4), 8.10 (m, 1, aromatic H-6).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.80; H, 4.65; N, 6.03.

The CCl_4 was removed from the mother liquor and the residual oil was crystallized from MeOH to give the *trans*-7-nitro acetate **4d**: mp 82.5–83.5°; ir (KBr) 1730 (C=O), 1525 and 1340 (NO_2); nmr ($CDCl_3$) δ 1.54 (d, 3, J = 6 Hz, $CHCH_3$), 2.11 (s, 3, $OCOCH_3$), 5.09 (octet, 1, J = 6 and 2 Hz, $CHCH_3$), 5.98 (d, 1, J = 2 Hz, CHOAc), 7.08 (t, 1, J = 8 Hz, aromatic H-5), 7.79 (m, 1, aromatic H-4), 8.17 (m, 1, aromatic H-6).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.39; H, 4.79; N, 6.11.

***cis*-7-Dimethylamino-3-acetoxy-2-methyl-2,3-dihydrobenzofuran (5).**—The nitro acetate **4c** (1.5 g, 6.3 mmol) in a minimum amount (10–20 ml) of 2-methoxyethanol was added to a suspension of 10% Pd/C (1.0 g) and CH_2O (9 ml of a 37% aqueous solution) in MeOH (50 ml). The reaction mixture was stirred at 25° under a H_2 atmosphere (1 atm) until 774 ml (31.5 mmol) had been absorbed. The reaction mixture was filtered, concentrated to ~30 ml, and poured into $CHCl_3$ (100 ml). The $CHCl_3$ solution was washed with 5% $NaHCO_3$ (three 40-ml portions) and dried ($MgSO_4$), and the solvent was removed to give a yellow residual oil. An aliquot (200 mg) of the oil was chromatographed on a preparative tlc plate (10% EtOAc–Skelly B). The major band (uv visualization, R_f *ca.* 0.4–0.5) was removed and extracted with Et_2O. The solvent was evaporated and the residual oil was dissolved in anhydrous Et_2O and dried ($MgSO_4$). Dry HCl was passed into the solution to give the hydrochloride salt of **5** as a gum which solidified on standing. The solid was recrystallized from Me_2CO–EtOAc, mp 145.5–146.5°.

Anal. Calcd for $C_{13}H_{18}ClNO_3$: C, 57.45; H, 6.69; N, 5.15. Found: C, 57.64; H, 6.72; N, 5.37.

***cis*-7-Dimethylamino-3-hydroxy-2-methyl-2,3-dihydrobenzofuran (6).**—The amino acetate **5** (1.5 g, 6.3 mmol) was dissolved in MeOH (20 ml), and NH_4OH (10 ml) was added. The reaction mixture was stirred at 55° for 2 hr, cooled, and poured into H_2O (50 ml). The solution was extracted with $CHCl_3$ (three 50-ml portions) and the combined extracts were dried ($MgSO_4$). Evaporation of the solvent gave a dark residual oil which was chromatographed over 100 g of Woelm Al_2O_3 (activity grade I, neutral, 0.5% MeOH–C_6H_6). The fractions containing the product (on the basis of tlc) were combined and the solvent was removed to give a light yellow oil. Conversion of the residue to the HCl salt in Et_2O and recrystallization from Me_2CO–EtOAc gave **6**, mp 142–143° (62%).

Anal. Calcd for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.01; N, 6.10. Found: C, 57.57; H, 7.02; N, 6.06.

The methiodide salt **7** was prepared by dissolving **6** in absolute EtOH (10 ml), and CH_3I (1.0 ml) was added. The solution was refluxed for 30 min and then allowed to cool to room temperature. The salt which crystallized was analytically pure (70% yield): mp 191–192° nmr (D_2O) δ 1.58 (d, 3, J = 6 Hz, CCH_3), 3.72 (s, 9, NCH_3), 4.96 (quintet, 1, J = 6 Hz, $CHCH_3$), 5.28 (d, 1, J = 6 Hz, CHOAc), 7.0–7.3 (m, 1, aromatic H-5), and 7.5–7.8 (m, 2, aromatic, H-4 and H-6).

Anal. Calcd for $C_{12}H_{18}INO_2$: C, 42.99; H, 5.42; N, 4.18. Found: C, 42.99; H, 5.42; N, 4.07.

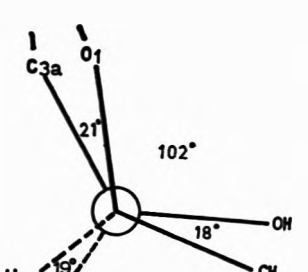


Figure 3.—Torsion angles from X-ray crystal structure of 7-trimethylammonium 3-hydroxy-2-methyl-2,3-dihydrobenzofuran iodide (**7**). Hydrogens are represented in presumed conformation.

Registry No.—**4a**, 26819-61-4; **4b**, 26819-62-5; **4c**, 26819-63-6; **4d**, 26921-99-3; **5** HCl, 28506-57-2; **6** HCl, 28506-58-3; **7**, 26819-65-8.

(10) All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind., or by Mrs. H. Kristiansen at the University of Kansas. Spectra were recorded on a Beckman IR-10, a Varian A-60A, a Varian HA 100, or a Finnigan 1015 mass spectrometer.

Photolysis of 2-(Benzyloxy)-4-(dodecyloxy)benzophenone and 2-Isopropoxy-4-methoxybenzophenone

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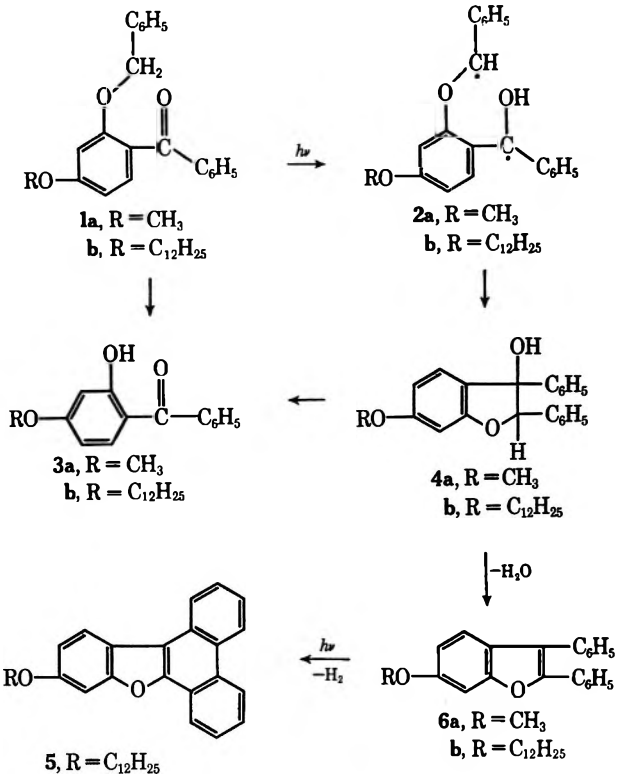
The photolysis of 2-(benzyloxy)-4-(dodecyloxy)benzophenone (**1b**) or of 2-isopropoxy-4-methoxybenzophenone (**9**) proceeded mainly *via* ring closure between the carbonyl carbon and the α carbon of the 2 substituent to give 6-(dodecyloxy)-2,3-dihydro-2,3-diphenyl-3-benzofuranol (**4b**) or 2,3-dihydro-2,2-dimethyl-6-methoxy-3-phenyl-3-benzofuranol (**12**), respectively. The quantum efficiencies for disappearance of starting ketone and for cyclization decreased significantly with an increase in solvent polarity. The lifetime of the excited state, believed to be $^3(n,\pi^*)$, was about 3×10^{-8} sec, unusually short for a benzophenone. Further photolysis of **1b** or **4b** resulted in dehydration to give 6-(dodecyloxy)-2,3-diphenylbenzofuran (**6a**) and partial cyclization of **6a** to 11-(dodecyloxy)-benzo[*b*]phenanthro[9,10-*d*]furan (**5**), but further photolysis of **12** gave only 2-hydroxy-4-methoxybenzophenone. Both **1b** and **9** gave the corresponding 4-alkoxy-2-hydroxybenzophenone as a minor product.

In a preliminary communication we reported that the photolysis of 2-(benzyloxy)-4-methoxybenzophenone (**1a**) gave 6-methoxy-2,3-diphenylbenzofuran (**6a**) and a small amount of 2-hydroxy-4-methoxybenzophenone (**3a**).[1] We now report a further investigation of the photochemistry of two 2,4-dialkoxybenzophenones, 2-(benzyloxy)-4-(dodecyloxy)benzophenone (**1b**) and 2-isopropoxy-4-methoxybenzophenone (**9**). Because the nature of the 4-alkoxy group has no significant effect on the photochemistry of **1** or **9**, these specific compounds were chosen for experimental convenience. The reaction products from **1b** were more easily separated than those from **1a**. The 4-methoxy substituent in **9** facilitated identification of the products by nmr analysis.

Results and Discussion

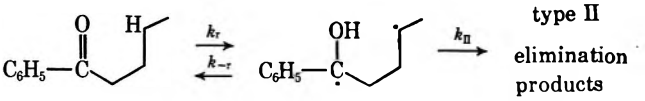
Photolysis of 2-(Benzyloxy)-4-(dodecyloxy)benzophenone (1b).—The photolysis of **1b** in cyclohexane (310 nm, 7 hr) gave 6-(dodecyloxy)-2,3-dihydro-2,3-diphenyl-3-benzofuranol (**4b**) in 67% yield (ϕ = 0.56) and 4-(dodecyloxy)-2-hydroxybenzophenone (**3b**) in 6% yield (ϕ = 0.07). Although benzyl phenyl ether[2] and other alkoxybenzenes undergo photorearrangement to 2- and 4-alkylphenols, no products of such a rearrangement of **1b** were found. Prolonged photolysis of **1b** (310 nm, 87 hr) or of **4b** (310 nm, 29 hr) resulted in dehydration to the benzofuran **6b** in high yield and a partial cyclization of this compound to 11-(dodecyloxy)benzo[*b*]phenanthro[9,10-*d*]furan (**5**). A small amount of **3b** was also found. The analogous photocyclization of 2,3-diphenylfuran has been reported.[3] These reactions are shown in Scheme I.

SCHEME I
PHOTOLYSIS OF 1



The ultraviolet spectrum of **1b** (Figure 1) is similar to that of benzophenone except that in hexane the (n,π^*) band [uv max 340 nm (ϵ 380)] is a shoulder on the (π,π^*) band [uv max 307 nm (ϵ = 6485)]. Because the photocyclization of **1b** proceeds efficiently at 360 nm and can be completely quenched by 2 *M* piperylene, the reaction probably proceeds from the $^3(n,\pi^*)$ by intramolecular abstraction of a benzylic hydrogen to give the diradical **2b** which collapses to **4b**. A similar mechanism has been proposed for the photocyclization of 4,6-di-*tert*-butyl-2-methoxybenzophenone to give 5-*tert*-butyl-7-methoxy-3,3-dimethylindan-1-ol, except that in the latter reaction hydrogen is abstracted from a methyl group of the *tert*-butyl moiety.[4]

The effect of solvent polarity on the photolysis of **1b** (Table I) was unexpected. Both the quantum efficiency for disappearance of **1b**, ϕ_d, and the quantum efficiency for cyclization to **4b**, ϕ_c, decrease by a factor of more than 3 as the solvent polarity increases in this series. This solvent effect is the reverse of that observed by Wagner for the type II photoelimination reaction of valerophenone which proceeds through a biradical similar to **2b**.[5]



(1) G. R. Lappin and J. S. Zannucci, *Chem. Commun.*, 1113 (1969).
(2) D. P. Kelly, J. T. Pinkey, and R. D. Rigby, *Tetrahedron Lett.*, 5953 (1966).
(3) A. Padwa and R. Hartman, *J. Amer. Chem. Soc.*, **88**, 3759 (1966).
(4) E. J. O'Connell, Jr., *ibid.*, **90**, 6550 (1968).
(5) P. J. Wagner, *ibid.*, **89**, 5898 (1967).

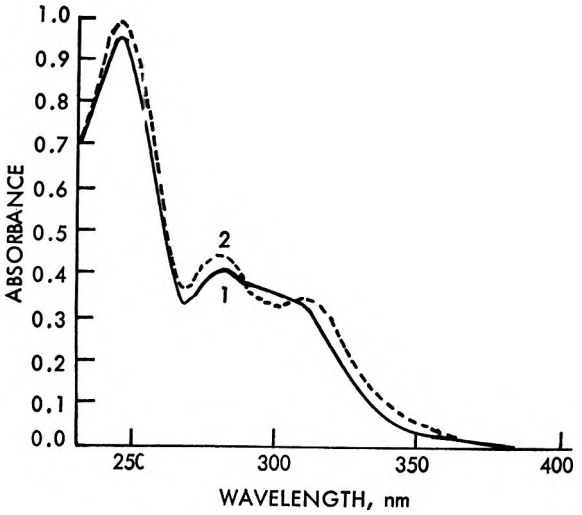


Figure 1.—Absorption spectra (0.100 g/l., 0.25-cm cell) of (1) 2-(benzyloxy)-4-(dodecyloxy)benzophenone, and (2) 4-(dodecyloxy)-2-isopropoxybenzophenone.

TABLE I

QUANTUM EFFICIENCIES AND TRIPLET LIFETIMES FOR PHOTOLYSIS OF 1b IN VARIOUS SOLVENTS

Solvent	ϕ_d[a]	ϕ_c[b]	$\tau \times 10^8$ sec[c]	ϕ_{ic}[d]
Cyclohexane	0.70	0.56		
Benzene	0.69	0.54	4.8	0.84
Dichloromethane	0.57	0.35		0.78
Acetone	0.38	0.22	2.3	
Acetonitrile	0.23	0.13	2.5	0.70
tert-Butyl alcohol	0.21	0.12	2.3	

[a] ϕ_d is for disappearance of **1b**. [b] ϕ_c is for appearance of **4b**. [c] Obtained from Stern–Volmer plots for piperylene quenching. Diffusion controlled quenching was assumed, and k_{diff} was calculated from η by using the Debye equation. [d] ϕ_{ic} is quantum efficiency for intersystem crossing as measured by sensitization of piperylene isomerization.

Wagner attributed the increase in quantum efficiency for elimination from 0.46 in hexane to 1.0 in acetonitrile to solvation of the hydroxyl hydrogen in the biradical, which impeded back abstraction of the hydrogen to regenerate valerophenone, thus reducing k_{-r}. Solvent polarity should have little effect on k_{II}; hence, the efficiency of the type II elimination was greatly increased in polar solvents.

Four possible explanations were considered for the decrease in ϕ_d and ϕ_c observed in polar solvents. First, in polar solvents an inversion of excited states might occur; this inversion would result in the population of the unreactive $^3(\pi,\pi^*)$. For acetophenone, Lamola found the first excited triplet to be $^3(n,\pi^*)$ in nonpolar solvents but the $^3(\pi,\pi^*)$ was lowest lying in polar solvents.[6] Such an inversion of excited states might be expected for **1b** because the lowest lying triplet for acetophenones substituted with methoxyl has been shown to be $^3(\pi,\pi^*)$.[7] Second, the observed effect of solvent polarity on the photolysis of **1b** might also arise from inefficient intersystem crossing to the triplet in polar solvents. Third, the reaction of the $^3(n,\pi^*)$ of **1b** might lead to different products in polar solvents than in nonpolar solvents. Finally, interaction between the polar solvent and the biradical **2b** might affect the relative importance of cyclization and return to the ground state but with results apparently opposite to those observed by Wagner.

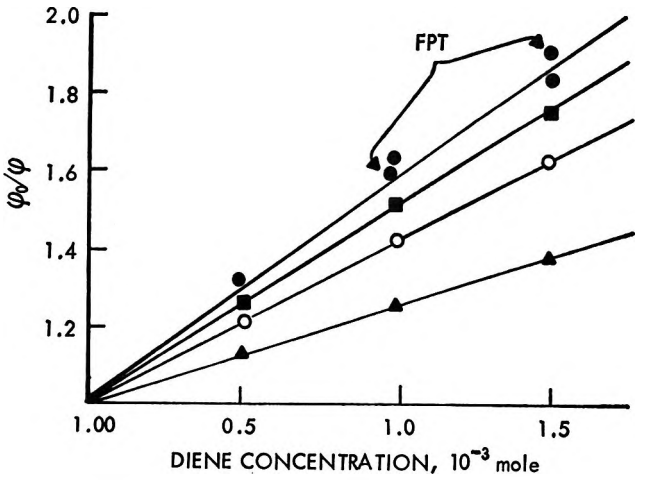


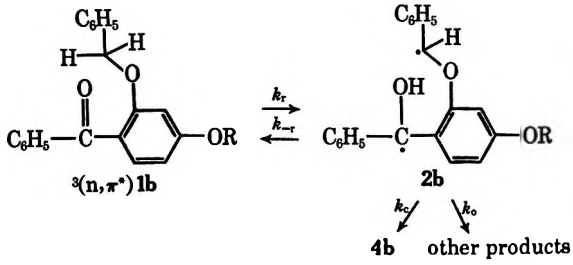
Figure 2.—Stern–Volmer plot for quenching photolysis of **1b** by *cis*-piperylene in acetonitrile (●), benzene (○), acetone (■), and *tert*-butyl alcohol (△). FPT: these two points were determined by freeze–pump–thaw degassing; all other points were determined by nitrogen-flow degassing.

To choose among these alternatives, we determined triplet lifetimes and the efficiencies of intersystem crossing for the photolysis of **1b** in benzene, acetone, acetonitrile, and *tert*-butyl alcohol. Linear Stern–Volmer plots (Figure 2) were obtained for photolysis of **1b** in the presence of *cis*-piperylene in all four solvents. These data led to nearly the same triplet lifetime ($\tau \approx 3 \times 10^{-8}$ sec) in the four solvents (Table I). Wagner and Kemppainen found that the triplet lifetime for valerophenone was increased from 7.1×10^{-9} sec for the parent compound to 4.5×10^{-7} sec for *p*-methoxyvalerophenone and attributed this to a change from $^3(n,\pi^*)$ to $^3(\pi,\pi^*)$ for the lowest excited state in *p*-methoxyvalerophenone.[8] If the triplet of **1b** had $^3(\pi,\pi^*)$ character in polar solvents, τ should have increased significantly. Our data show a small decrease in τ in polar solvents; hence, the same excited state of **1b** is involved in its reactions in either polar or nonpolar solvents. Although Kearns found the lowest excited state of *p,p'*-dimethoxybenzophenone to be $^3(n,\pi^*)$,[9] we considered the possibility that the lowest triplet for **1b** was $^3(\pi,\pi^*)$ in both polar and nonpolar solvents. However, the phosphorescence lifetime of **1b** in either EPA (5.4×10^{-3} sec) or 1:1 heptane–pentane (3.2×10^{-3} sec) is of the magnitude expected for a benzophenone $^3(n,\pi^*)$ (*ca.* 10^{-3} sec) rather than that expected for the $^3(\pi,\pi^*)$ (*ca.* 1 sec).[10] These results confirm our conclusion that the $^3(\pi,\pi^*)$ makes no significant contribution to the photochemistry of **1b**. Triplet counting by the piperylene isomerization technique[11] did show a small decrease in the efficiency of intersystem crossing, ϕ_{ic} (Table I), but this effect was too small to account for the large solvent effect we observed. Product analysis showed no observable effect of solvent polarity on the photolysis products of **1b**; hence, a change in reaction path cannot account for the solvent

(6) A. A. Lamola, *J. Chem. Phys.*, **47**, 4810 (1967).
(7) T. Takemura and H. Baba, *Bull. Chem. Soc. Jap.*, **42**, 2756 (1969).
(8) P. J. Wagner and A. E. Kemppainen, *J. Amer. Chem. Soc.*, **90**, 5898 (1968).
(9) D. R. Kearns and W. A. Case, *ibid.*, **88**, 5087 (1966).
(10) N. C. Yang, D. S. McClure, S. L. Murov, J. J. Houser, and R. Dusenbery, *ibid.*, **89**, 5466 (1967).
(11) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

effect. We conclude, therefore, that the biradical **2b** is formed with high efficiency in both polar and nonpolar solvents and that the observed effect of solvent polarity occurs because of interaction between **2b** and the polar solvent. Whether solvation of a diradical intermediate leads to an increase in ϕ_d, as observed by Wagner,[5] or to a decrease in ϕ_d, as we report, for a ketone depends on the nature of the reaction paths available to the two radicals.

We propose the following mechanistic scheme for the photolysis of **1b**.

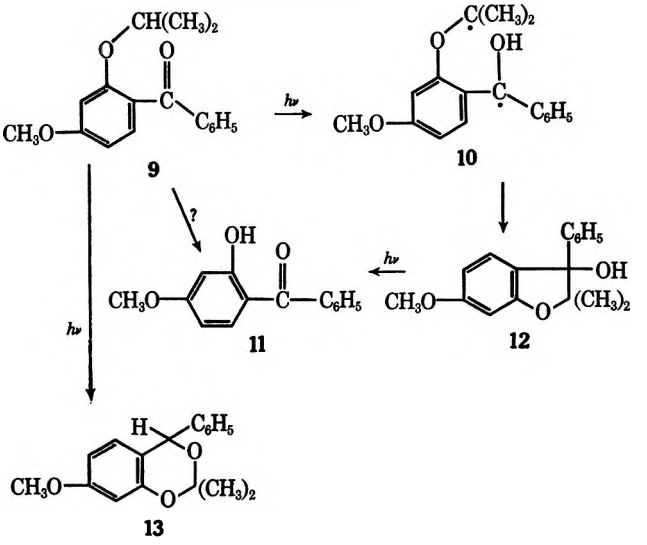


The intramolecular hydrogen abstraction (**1b*** → **2b**) involves a seven-membered transition state and so should be very rapid. Thus, the lifetime of the triplet state of **1b** should be shorter than the expected lifetime for a benzophenone triplet ($\tau \approx 10^{-6}$ sec) where intermolecular hydrogen abstraction is involved in accord with our observation of $\tau \approx 3 \times 10^{-8}$ sec. In nonpolar solvents, **2b** efficiently cyclizes to **4b** ($k_c \gg k_{-r}$). Solvation of **2b** by a polar solvent should reduce k_{-r} by interference with the back abstraction of hydrogen, as it does for valerophenone. However, the effect of a reduction in k_{-r} on the disappearance of starting ketone depends on what alternative reaction paths are available to the biradical. The biradical from valerophenone has available a facile elimination reaction which can proceed without regard to any particular molecular orientation or solvent effect; hence, the loss of valerophenone becomes more efficient when k_{-r} is reduced. For **3b**, the only significant alternative to reverse hydrogen abstraction is cyclization. It seems reasonable that solvation of **3b** would also reduce k_c, because the solvent sheath might well impede assumption of the geometry necessary for cyclization. Indeed, Wagner, observed a similar effect in the cyclization of valerophenone to a cyclobutanol, which occurred as a minor side reaction competing with elimination.[5] If k_c is decreased more than k_{-r} in polar solvents and if k_0, the rate of formation of all other products, remains relatively unchanged, then the rate at which **1b** disappears will decrease in polar solvents. The effect of polar solvents, although it arises from the same interaction of solvent and biradical, becomes the reverse of that observed by Wagner.

Photolysis of 2-Isopropoxy-4-methoxybenzophenone (9).—Photolysis of **9** in benzene (310 nm, 7 hr) gave not only the products expected from the results with **1b**, 2,3-dihydro-6-methoxy-2,2-dimethyl-3-phenyl-3-benzofuranol (**12**, 44% yield) and 2-hydroxy-4-methoxybenzophenone (**11**, 14% yield), but an unexpected product, 7-methoxy-2,2-dimethyl-4-phenyl-1,3-benzodioxane (**13**) in 28% yield (Scheme II). No product analogous to **13** was detected in the photolysis of **1b**; hence, some reaction path which is available to **9** is not available to **1b**. The effect of solvent polarity was less extensively studied for **9** than for **1b**, but the

SCHEME II

PRODUCTS FROM PHOTOLYSIS OF 9



SCHEME III

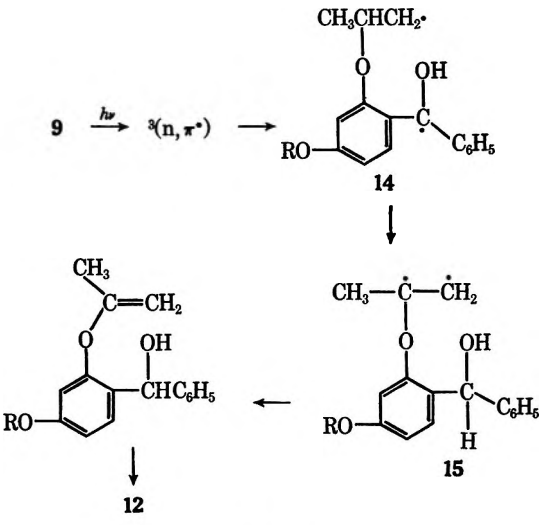


TABLE II

QUANTUM EFFICIENCIES FOR THE PHOTOLYSIS OF 9 IN CYCLOHEXANE AND ACETONITRILE

Solvent	ϕ_d[a]	ϕ_{12}[b]	ϕ_{13}[c]
Cyclohexane	0.51	0.26	0.15
Acetonitrile	0.14	0.023	0.005

[a] ϕ_d is for disappearance of **9**. [b] ϕ_{12} is for the appearance of **12**. [c] ϕ_{13} is for the appearance of **13**.

data in Table II show that polar solvents repress the loss of ketone and the cyclization to the benzofuranol to a greater extent than for **1b**. Cyclization to the 1,3-benzodioxane is decreased markedly in acetonitrile.

Although the cyclization to **12** undoubtedly involves the biradical **10**, the formation of **13** is less easily accounted for. It is not formed by a ring expansion of **12**; photolysis (310 nm, 24 hr) of **12** gave only **11** and unreacted **12**. In fact, the relative amounts of **11** formed by photolysis of **9** and **12** lead us to believe that the most of the **11** isolated in the photolysis of **9** is actually a secondary product arising from **12**. Bimolecular reactions involving hydrogen exchanges between **9** and the biradical **10** could also produce **13**. However, when the photolysis of **9** (benzene solution, 310 nm, 7 hr) was carried out over a range of concen-

trations from 0.002 *M* to 0.074 *M*, the ratio of **13** to **12** remained constant at 0.25; hence, any bimolecular reaction mechanism can be eliminated. Scheme III shows a tentative mechanism for the formation of **12**. The second intramolecular hydrogen abstraction (**14** → **15**) involves a six-membered transition state and should occur readily. This mechanism accounts for the failure of **1b** to give a product analogous to **13**.[12] However, we cannot offer any unequivocal explanation for the formation of **13**.

Experimental Section

Preparation of 2-(Benzyloxy)-4-(dodecyloxy)benzophenone (1b).—Benzyl bromide (25.2 g, 0.2 mol) was added to a solution of 76 g (0.2 mol) of 4-(dodecyloxy)-2-hydroxybenzophenone and 11.2 g (0.2 mol) of potassium hydroxide in 500 ml of ethanol. This solution was refluxed for 18 hr and then evaporated to dryness in a rotary evaporator. The residue was extracted with 200 ml of ether, and the ether solution was extracted twice with 50-ml portions of 10% aqueous NaOH solution and then twice with 50 ml of water. The ethereal extract was dried over anhydrous Na_2SO_4 and concentrated. The residue was recrystallized twice from ethanol to give 63 g (67%) of **1b**, mp 56–58°.

Anal. Calcd for $C_{32}H_{40}O_3$: C, 81.40; H, 8.47. Found: C, 81.59; H, 8.55.

Preparation of 2-Isopropoxy-4-methoxybenzophenone (9).—This compound was prepared in the same way as **1b** from 45.6 g (0.2 mol) of 2-hydroxy-4-methoxybenzophenone and 24.6 g (0.2 mol) of 2-bromopropane. The yield of white crystals was 23 g (46%), mp 57–59°.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.59; H, 6.67. Found: C, 75.35; H, 6.60.

General Irradiation Procedure.—Benzene was washed with sulfuric acid and with water, dried over $MgSO_4$, and distilled. All other solvents were dried over $MgSO_4$ and distilled.

Samples were irradiated under nitrogen in 12-mm-o.d. Pyrex glass tubes closed by a serum cap. Dissolved oxygen was removed by bubbing nitrogen (20 ml/min) through 6 ml of solution from a 27-gage hypodermic needle for 2 min.[13] Piperylene quenching and triplet counting experiments (Table I) were carried out in a "merry-go-round." The light source was a Hanovia 550-W medium-pressure arc; the 366-nm band was isolated by Corning 0-52 and 7-37 filters in series. Piperylene isomers were analyzed by glc on a $\frac{1}{8}$ in. × 30 ft column packed with 25% 3,3′-oxydipropionitrile on 60–80-mesh Chromosorb P solid support. **1b** and **4b** (data in Table I) were determined by glc at 310° on a 0.25 in. × 10 ft column packed with 25% Lexan polycarbonate on 40–60-mesh Chromosorb W solid support. The data for the disappearance of **9** were also obtained with this glc column under the same conditions. Quantum yields were determined by uranyl oxalate actinometry.[14] A Rayonet photochemical reactor fitted with 310-nm lamps was used for all other irradiations.

Photolysis of 2-(Benzyloxy)-4-(dodecyloxy)benzophenone (1b). A.—A solution of 500 mg of **1b** in 100 ml of cyclohexane was irradiated for 7 hr. The yellow solution was concentrated to a small volume and chromatographed on two 20 cm × 20 cm × 2 mm silica gel thin layer plates with 1:1.5 isooctane–methylene chloride mixture. The clear oil, 338 mg (67.5%), which was obtained was crystallized from ethanol to yield a white, crystalline material, mp 64–65°, identified as 6-(dodecyloxy)-2,3-dihydro-2,3-diphenyl-3-benzofuranol (**4b**): nmr ($CDCl_3$) δ 6.2–7.6 (m, 13 H, aromatic), 5.60 (s, 1 H, benzylic), 3.95 (m, 2 H, CH_2O), 2.25 (s, 1 H, OH), 1.25 (2 OH, CH_2), and 0.90 (t, 3 H, CH_3).

Anal. Calcd for $C_{32}H_{40}O_3$: C, 81.40; H, 8.47. Found: C, 81.69; H, 8.52.

Also isolated was 30 mg (6%) of 4-(dodecyloxy)-2-hydroxybenzophenone (**3b**), mp 50–52°. Mixture melting point and ir were identical with those of an authentic sample.

B.—**1b** (3.0 g) in hexane (100 ml) was irradiated for 87 hr. The yellow solution was evaporated to a small volume, cooled (−70°), and filtered. Decolorization and recrystallization from hexane (−70°) furnished 0.32 g (10.5%), mp 104–105°, of a white crystalline material identified as 11-(dodecyloxy)benzo[*b*]phenanthro[9,10-*d*]furan (**5**): nmr ($CDCl_3$) δ 7.1–8.8 (m, 9 H, aromatic), 7.10 (d, 1 H, aromatic), 6.91 (q, 1 H, aromatic), 3.95 (t, 2 H, CH_2O), 1.25 (2 OH, CH_2), and 0.87 (t, 3 H, CH_3). The mass spectrum had a parent ion peak at *m/e* 452 (M − 20).

Anal. Calcd for $C_{32}H_{36}O_2$: C, 85.00; H, 8.41. Found: C, 85.00; H, 8.29.

The combined hexane fractions from the above precipitation were evaporated to dryness, and the residue was then dissolved in a small volume of ethanol, cooled to −70°, and filtered. A second recrystallization furnished 1.9 g (63.5%) of a white, crystalline material identified as 6-(dodecyloxy)-2,3-diphenylbenzofuran (**6b**): mp 62–64°; nmr ($CDCl_3$) δ 7.0–7.8 (m, 11 H, aromatic), 6.96 (d, 1 H, aromatic), 6.75 (q, 1 H, aromatic), 3.95 (t, 2 H, CH_2O), 1.25 (2 OH, CH_2), and 0.90 (t, 3 H, CH_3). The mass spectrum had a parent ion peak at *m/e* 454 (M − 18, loss of water).

Anal. Calcd for $C_{32}H_{38}O_2$: C, 84.50; H, 8.37. Found: C, 84.38; H, 8.56.

Photolysis of 2-Isopropoxy-4-methoxybenzophenone (9).—A solution of 500 mg of **9** in 100 ml of benzene was irradiated for 7 hr. The yellow solution was evaporated to a paste, which was taken up in a small quantity of acetone and chromatographed on two 20 cm × 20 cm × 2 mm silica gel thin layer plates with 1:1.5 isooctane–methylene chloride. The plates were divided into three bands, top, center, and bottom, and eluted with acetone.

The top band (140 mg, 28%) was recrystallized from ethanol at −70°. The white, crystalline material obtained, mp 104–107°, was identified as 7-methoxy-2,2-dimethyl-4-phenyl-1,3-benzodioxane (**13**). The mass spectrum included, in addition to the parent ion peak at *m/e* 270, a predominant peak at *m/e* 212 (M − 58, loss of acetone); nmr spectrum ($CDCl_3$) δ 7.29 (s, 5 H, aromatic), 7.1 (m, 1 H, aromatic), 6.25–6.6 (m, 2 H, aromatic), 5.74 (s, 1 H, benzylic), 3.70 (s, 3 H, OCH_3), and 1.61 (s, 6 H, geminal dimethyl).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.59; H, 6.67. Found: C, 75.70; H, 6.81.

The center band (70 mg, 14%) was recrystallized from ethanol, mp 62–64°. Mixture melting point and ir spectrum were identical with those of an authentic sample of 2-hydroxy-4-methoxybenzophenone.

The bottom band (220 mg, 44%) was recrystallized from ethanol at −70°, to yield a white, crystalline material, mp 122–123°, identified as 2,3-dihydro-6-methoxy-2,2-dimethyl-3-phenyl-3-benzofuranol (**12**): nmr ($CDCl_3$) δ 7.1–7.5 (m, 5 H, aromatic), 6.96 (d, 1 H, aromatic), 6.35–6.39 (m, 2 H, aromatic), 3.69 (s, 3 H, OCH_3), 2.25 (s, 1 H, CH_3), 1.53 (s, 3 H, CH_3), and 0.82 (s, 3 H, CH_3).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.59; H, 6.67. Found: C, 75.60; H, 6.77.

Photolysis of 2,3-Dihydro-6-methoxy-2,2-dimethyl-3-phenyl-3-benzofuranol (12).—A solution of 0.200 g of **12** in 50 ml of benzene was irradiated for 29 hr. The solution was concentrated and chromatographed as in the photolysis of **1b** to yield 0.106 g of starting material (53%) and 0.032 g (38%) of 2-hydroxy-4-methoxybenzophenone.

Registry No.—**1b**, 28856-48-6; **4b**, 28856-49-7; **5**, 28856-50-0; **6b**, 28856-51-1; **9**, 28856-52-2; **12**, 28856-53-3; **13**, 28856-54-4.

Acknowledgment.—The authors gratefully acknowledge the help of Professor David Whitten, of the University of North Carolina, with whom many fruitful discussions of this work were held.

(12) We have found that hydrogen abstraction from the carbon β to the ether function occurs in the photolysis of 4-methoxy-2-(2-phenylethoxy)-benzophenone, but the complex reaction mixture has not yet been resolved. The possibility that **13** was formed *via* reduction of **9** to the benzhydrol was also considered; however, when **9** was photolyzed in isopropyl alcohol, the major products appeared to be the benzhydrol and the pinacol. The reaction mixture could not be satisfactorily separated, but the nmr spectrum of the photolysis product showed that no **13** was present.

(13) The reliability of this method for oxygen removal was confirmed by comparison with the more tedious freeze–pump–thaw method. Quenching data from the two degassing procedures fell on the same line in the Stern–Volmer plot.

(14) C. R. Masson, V. Boekelheide, and W. A. Noyes, Jr., in "Catalytic, Photochemical, Electrolytic Reactions (Techniques of Organic Chemistry)," 2nd ed, Vol. II, A. Weissberger, Ed., Interscience, New York N. Y., 1965, pp 294–298.

Reactions of Steroidal 3,4-Diones (Diosphenols) with Ketalizing Agents[1,2]

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The reaction of 3 4-dioxo steroids (**1**) with ethylene glycol and *p*-toluenesulfonic acid, under ketalizing conditions, gave steroidal 3,5-dieno[3,4-*b*]dioxanes as well as the 5α- and 5β-4-oxo 3-ethylenedioxy ketals. 2-Mercaptoethanol reacted with 3,4-dioxocholestane (**1a**) to give 3,5-cholestadieno[4,3-*b*]oxathiane as well as four isomeric 4-oxo 3-ethylene monothioketals. Reaction of **1a** with 1,2-ethanedithiol gave 5α- and 5β-4-oxo 3-ethylene dithioketals, but no cholesta-3,5-dieno[3,4-*b*]dithiane was obtained. Base-catalyzed equilibration of the pairs of 4-oxo 3-ethylene monothioketals epimeric at C-5 favored, in each case, the isomer with equatorial oxygen in the monothioketal ring. In the case of the 3(*S*)-ethylene monothioketals of 5α- and 5β-cholestane-3,4-dione, the stability order (A/B trans favored over A/B cis) for cholestan-4-one was inverted, giving predominantly 5β-4-oxocholestane 3(*S*)-ethylene monothioketal.

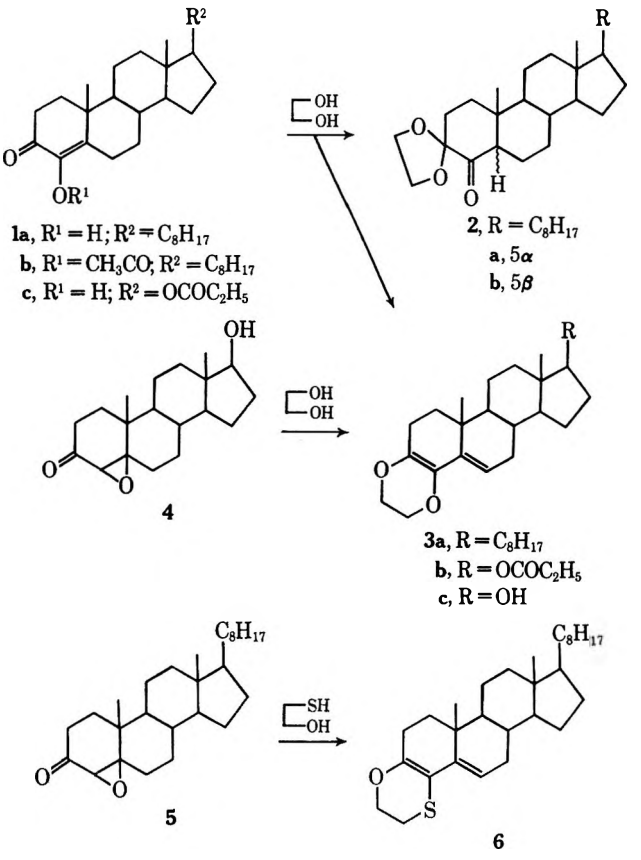
It has been reported[3] that 4,17-diacetoxy-4-androsten-3-one gives 3-ethylenedioxy-4,17-diacetoxyandrost-4-ene under ketalizing conditions (benzene–ethylene glycol–*p*-toluenesulfonic acid). Our need for 4-oxo steroids bearing a protected C-3 oxygen substituent led us to reexamine the above reaction.

We found that both 4-hydroxy-4-cholesten-3-one[4] (**1a**) and the corresponding 4-acetoxy compound[5] **1b** gave 3,5-cholestadieno[3,4-*b*]dioxane (**3a**) in about 30% yield under the standard ketalizing conditions mentioned above, although some ketalization at C-3 also occurred (*vide infra*). The structural assignment for **3a** is supported by analytical and spectroscopic data. Further support comes from analogy with the 2-mercaptoethanol ketalizations to be discussed latter.

Using somewhat different ketalizing conditions (2-methyl-2-ethyl-1,3-dioxolane), we found that 17β-propionoxy-4-hydroxy-4-androsten-3-one (**1c**) gave the analogous [3,4-*b*] dioxane **3b**. The latter compound had spectroscopic properties closely similar to those of compound **3a**, and the mass spectrum of **3b** showed a strong molecular ion peak at *m/e* 386, with a strong fragment peak at *m/e* 358 (probably due to loss of ethylene). Furthermore, reaction of 17β-hydroxy-4,5β-oxidoandrostan-3-one (**4**) with ethylene glycol–benzene–*p*-toluenesulfonic acid gave 17β-hydroxy-3,5-androstadieno[3,4-*b*]dioxane (**3c**). Propionylation at C-17 of the latter compound gave **3b**, identical with the same product obtained from the diosphenol **1c** (see Scheme I).

It is known[6] that 4,5β-oxido-3-oxo steroids react with 2-mercaptoethanol or 1,2-ethanedithiol in polyphosphoric acid to give $\Delta^{3,5}$-dieno[3,4-*b*]oxathianes or dithianes. In these cases, reaction is presumably initiated by oxide protonation and nucleophilic attack on C-4 by sulfur. Indeed, we found that, under our reaction conditions (benzene and *p*-toluenesulfonic acid), 4,5β-oxidocholestan-3-one[7] (**5**) gave, with 2-mercaptoethanol, the known 3,5-cholestadieno[3,4-*b*]-oxathiane (**6**). However, under the same conditions, 4-hydroxy-4-cholesten-3-one (**1a**) gave none of this latter product **6** but instead furnished the *isomeric* 3,5-cholestadieno[4,3-*b*]oxathiane (**7**).

SCHEME I



Analytical data and infrared, nmr, and mass spectra were all consistent with structure **7**, and chemical support came from reduction of compound **7** with Raney nickel to 4-ethoxy-3,5-cholestadiene (**9**). The hitherto undescribed enol ether **9** was readily cleaved by aqueous acetic acid to the known[8] 5-cholesten-4-one (**10**), securing the structure of **9** and hence of the [4,3-*b*]oxathiane **7**.

The acid-catalyzed conversion of α,β-epoxy ketones to diosphenols (*e.g.*, **5** to **1a**) is well documented,[9] and the formation of the $\Delta^{3,5}$-dieno[3,4-*b*]dioxane system

(1) This work was supported in part by U. S. Public Health Service Grant HE-08913 and by GM-16492.

(2) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstracts, O-67.

(3) B. Camerino, D. Catapan, U. Valcavi, and B. Patelli, *Gazz. Chim. Ital.*, **89**, 674, (1959).

(4) A. Butenandt, G. Schramm, A. Wolff, and H. Kudszus, *Chem. Ber.*, **69**, 2779 (1936).

(5) L. F. Fieser and R. Stevenson, *J. Amer. Chem. Soc.*, **76**, 1728 (1954).

(6) M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka, and T. Furuta, *Chem. Pharm. Bull.*, **12**, 383 (1964); *Tetrahedron*, **21**, 733 (1965).

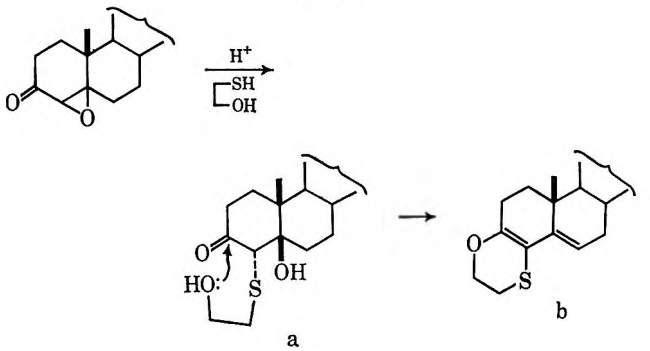
(7) P. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).

(8) A. Butenandt and A. Wolff, *Chem. Ber.*, **68**, 2091 (1935).

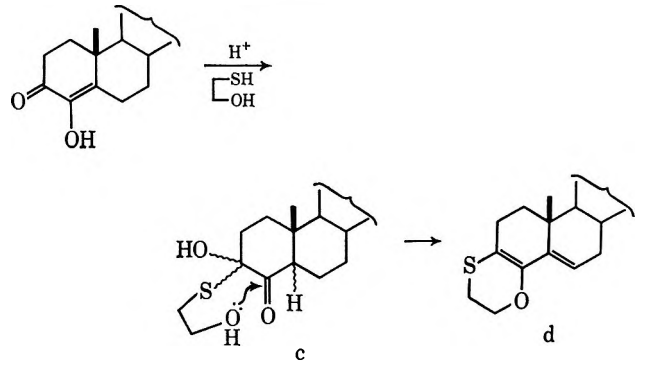
(9) *Cf.* B. Camerino, B. Patelli, and A. Vercellone, *J. Amer. Chem. Soc.*, **78**, 3540 (1956).

(3) from both the diosphenol **1c** and the α,β-epoxy ketone **4** with ethylene glycol and acid might have been so explained. However, the 2-mercaptoethanol experiments which have just been described show that, whereas the α,β-epoxy ketone undergoes nucleophilic attack first at C-4, the diosphenol reacts first at C-3 (see Schemes II and III).

SCHEME II



SCHEME III



Thus, in Scheme II, the adduct a can generate the product b *via* attack of hydroxyl oxygen at C-3, with subsequent acid-catalyzed dehydrations. In Scheme III, attack by sulfur at C-3 with subsequent ketonization of the Δ^4 enol can lead to c. The latter could then form product d by attack of oxygen on the newly formed C-4 carbonyl, with subsequent dehydration.

The reaction of the diosphenol **1a** with 2-mercaptoethanol, which gave the [4,3-*b*]oxathiane (**7**) discussed above, in approximately 10% yield, also furnished four crystalline monothioketals. These are formulated as the four possible isomers (**8a–d**) of cholestane-3,4-dione 3-ethylene monothioketal, for the following reasons.

The analytical data for each compound supported the gross composition, $C_{29}H_{48}O_2S$, and the infrared spectrum of each compound showed absorption attributable to a carbonyl group in a six-membered ring. Two of these compounds, **8b** and **8c**, were further characterized as the sulfones (**15** and **16**, respectively), obtained by oxidation with *m*-chloroperbenzoic acid. The mass spectra of compounds **8a–d** *were indistinguishable* and have been discussed in detail elsewhere.[10] The nmr spectra of compounds **8a–d** were also entirely consistent with the structures assigned and permitted assignment of stereochemistry at C-5. Thus, compounds **8a** and **8b** had resonances at δ 0.72 and 0.73, respectively, for their C-19 methyl groups, whereas compounds **8c** and **8d** each showed the C-19 methyl resonance at δ 1.09. The C-19 methyl protons in 5α-cholestan-4-one appear at δ 0.75, while in 5β-cholestan-4-one the C-19 methyl resonance occurs at δ 1.12, the large difference being attributable to the shielding and deshielding effect, respectively, of the carbonyl group in *trans*- and *cis*-4-oxo steroids. Assuming no serious effects due to the ketal grouping at C-3 in compounds **8a–d**, the above data classify compounds **8a** and **8b** as 5α- and compounds **8c** and **8d** as 5β-4-oxocholestane derivatives. The assumption that the 3-ketal grouping has no substantial perturbing effect was supported by the nmr data for the pairs of 3-ethylenedioxy ketal and 3-ethylene dithioketal derivatives of cholestan-4-one (**2a,b**, and **11a,b**, respectively) whose preparation and properties are discussed later.

Although the nmr data permitted us to conclude that compounds **8a** and **8b** were 5α- and that **8c** and **8d** were 5β-cholestan-4-one derivatives, the stereochemistry at C-3 was still unknown. This problem was attacked by two independent methods, the first of which was ORD and CD measurements. These data allowed conclusive assignment of stereochemistry at C-3 for compounds **8a–d** and have been discussed in detail elsewhere.[11]

The second approach involved reduction of the 5α-cholestan-4-one 3-monothioketals **8a** and **8b** with hydride to give the 4β (axial) alcohols **14a** and **14b**. In one case there should be intramolecular hydrogen bonding between the axial 4β-hydroxyl group and equatorial sulfur at C-3, and in the other the hydrogen bonding would be between the axial 4β-hydroxyl group and equatorial oxygen at C-3. Infrared measurements should then settle the configuration at C-3, given suitable models, which were synthesized as follows.

Reaction of 4-hydroxy-4-cholesten-3-one (**1a**) with 1,2-ethanedithiol in benzene, with *p*-toluenesulfonic acid catalyst, gave both 5α- and 5β-cholestane-3,4-dione 3-ethylene dithioketal (**11a** and **11b**, respectively) which were separated readily by chromatography. When the reaction was monitored by tlc, it became clear that the 5β isomer **11b** is the kinetically controlled product which equilibrates under the acidic reaction conditions to give the more stable 5α isomer **11a**. Interestingly, we could not detect any product with the ultraviolet absorption of a 3,5-cholestadieno[3,4-*b*]dithiane. Equilibration of **11a** and **11b** with base gave a mixture containing preponderantly isomer **11a**.

Fieser and Stevenson had earlier reported[12] the formation of the 5β isomer **11b** by the action of 1,2-ethanedithiol–boron trifluoride on the diosphenol **1a** and had proved the configuration at C-5 by desulfurization to 5β-cholestan-4-one.

Reduction of the 5α isomer **11a** with sodium borohydride gave the expected 4β-hydroxy compound **12** in nearly quantative yield. Elemental analysis and the mass spectrum were consistent with structure **12**, and the nmr spectrum confirmed the equatorial nature of the C-4 hydrogen (width at half height, 5 Hz) and hence the axial nature of the C-4 hydroxyl. Desulfurization of compound **12** gave the known[13] 5α-cholestan-4β-ol providing final proof of structure and stereochemistry.

Similarly, reduction of 5α-cholestane-3,4-dione 3-ethylenedioxy ketal (**2a**) with sodium borohydride gave

(10) C. Fenselau, L. Milewich, and C. H. Robinson, *J. Org. Chem.*, **34**, 1374 (1969).

(11) C. H. Robinson, L. Milewich, G. Snatzke, W. Klyne, and S. R. Wallis, *J. Chem. Soc. C*, 1245 (1968).

(12) R. Stevenson and L. F. Fieser, *J. Amer. Chem. Soc.*, **78**, 1409 (1956).

(13) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

the 4β-ol **13** whose structure followed from analytical, mass spectroscopic, and nmr data and analogy with the reduction of compound **11a**. The 4-oxo 3-ethylenedioxy ketal **2a** had been isolated, along with the 5β isomer **2b**, from the reaction of 4-hydroxy-4-cholesten-3-one (**1a**) with ethylene glycol which gives mainly the [3,4-*b*]dioxane **3a** as already noted. The structures of the ketals **2a** and **2b** were established by analytical and spectroscopic data.

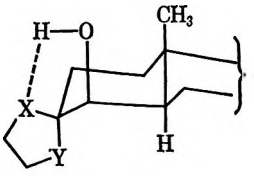
Before preparing the 4β-hydroxy 3-ethylene monothioketals, the hydroxyl stretching frequencies of the model compounds **12** and **13** were measured. The hydroxyl stretching frequency of 5α-cholestan-4β-ol, measured under the same conditions, was used as reference, and the data and $\Delta\nu$ values are given in Table I. Thus, for compound **12** where OH---S intramolecular hydrogen bonding must occur, $\Delta\nu = 86$ cm^{-1}, while for compound **13**, involving OH---O bonding, $\Delta\nu = 37$ cm^{-1}. These figures are in good agreement with data[14,15] from acyclic compounds for OH---S and OH---O intramolecular hydrogen bonding involving a quasi five-membered ring. We therefore set about the preparation of the 4β-hydroxy 3-ethylene monothioketals (**14a** and **14b**), which were readily obtained in nearly quantitative yield by borohydride reduction of the corresponding ketones **8a** and **8b**. The formulation of **14a** and **14b** as 4-hydroxy 3-ketals followed from their mode of preparation, and analytical and mass spectroscopic data, while the configuration at C-4 was assigned on the basis of the nmr spectra. Not only does the width at half height of the C-4 proton resonance confirm its equatorial nature, but the C-19 methyl resonances confirm the presence of a 4β- rather than a 4α-hydroxyl group. Whereas a 4β-hydroxyl substituent causes a marked downfield shift of the C-19 methyl resonance, a 4α-hydroxyl group has little effect.[16,17]

The hydroxyl stretching frequencies of the two monothioketals **14a** and **14b** were measured at high dilution (Table I) and $\Delta\nu$ values of 57 and 36 cm^{-1}, respectively, were recorded.

The latter value corresponds very closely to that for OH---O bonding in compound **13** and the $\Delta\nu$ for compound **14b**, while lower than that seen for OH---S bonding in compound **12**, is still significantly higher than that for the OH---O situation. The C-3 stereochemistry thereby deduced for compounds **14a** and **14b**, and hence for the parent 4-oxo compounds **8a** and **8b**, is in full accord with that established from CD-ORD studies.

Finally, the two remaining 5β-4-oxo 3-monothioketals **8c** and **8d** were matched with the appropriate 5α compounds **8a** and **8b** by equilibration experiments. These equilibrations, using methanolic potassium hydroxide showed that compounds **8a** and **8c** on the one hand, and **8b** and **8d** on the other, constituted pairs differing only in their stereochemistry at C-5. The C-3 stereochemistry thereby deduced for compounds **8c** and **8d** agreed with that assigned on the basis of CD-ORD data. The equilibration studies are of interest, because when epimerization at C-5 occurs in these compounds there is concomitant change from equatorial to axial (or *vice versa*) of the C-3 substituents.

TABLE I
INFRARED DATA[a] FOR 5α-CHOLESTAN-4β-OL 3-ETHYLENE KETALS



Compd	X	Y	ν_{OH}, cm^{-1}	$\Delta\nu$, cm^{-1}
5α-Cholestan-4β-ol			3629	
12	S	S	3543	86
14a	S	O	3572	57
13	O	O	3592	37
14b	O	S	3593	36

[a] Obtained for 10^{-3} *M* solutions in CCl_4, with 3-mm cells, using a Perkin-Elmer Model 521 spectrophotometer, calibrated against water vapor.

The equilibration of cholestan-4-one has been found[18] to result in a mixture of 99% of the 5α isomer (A/B trans) and 1% of the 5β isomer (A/B cis) using potassium hydroxide in methanol at 25°. Our equilibrations of the 4-oxo 3-hemithioketals **8a–d** were carried out using 10% potassium hydroxide in methanol at reflux, and we also equilibrated cholestan-4-one under these conditions, obtaining an equilibrium mixture of 83% 5α-cholestan-4-one and 17% 5β-cholestan-4-one. By comparison, the equilibrium between **8a** (X = S; Y = O) and **8c** (X = S; Y = O) (Scheme IV) resulted in *ca.* 87% of the 5β isomer **8c** and *ca.* 13% of the 5α isomer **8a**. On the other hand, compounds **8b** (X = O; Y = S) and **8d** (X = O; Y = S) (Scheme IV) gave an equilibrium mixture containing essentially only the 5α epimer **8b** with no detectable amounts of the 5β compound **8d**.

Equilibration of the 4-oxo 3-ethylenedioxy ketals **2a,b** and the corresponding 3-ethylene dithioketals **11a,b** gave in each case mixtures in which the 5α epimer greatly predominated as shown by tlc. However, these latter experiments were qualitative, and percentage values cannot be assigned.

Although for cholestan-4-one itself equilibrium lies far on the side of the A/B trans isomer, new nonbonded interactions can radically affect the equilibrium position and indeed this is so for 1,4-dioxo steroids.[19] In the latter case, unfavorable C-1, C-11 substituent interactions in the 5α compound are relieved in the 5β (A/B cis) isomer.

Our results with the ethylene monothioketals **8a–d** clearly involve the conformational preferences of the C-3 oxygen and sulfur substituents. Determinations of the effective relative sizes of oxygen and divalent sulfur in substituted cyclohexanes suggest that there should

(14) Dr. L. P. Kuhn (personal communication) has observed a $\Delta\nu$ value of 93 cm^{-1} for intramolecular OH---S bonding in 2-methylmerceptoethanol and of 32 cm^{-1} for intramolecular OH---O bonding in ethylene glycol.

(15) M. Mori, Y. Takahashi, and Y. Tsuzuki, *Bull. Chem. Soc. Jap.*, **40**, 2720 (1967), report a $\Delta\nu$ of 90 cm^{-1} for intramolecular OH---S bonding in 2-ethylmercaptoethanol.

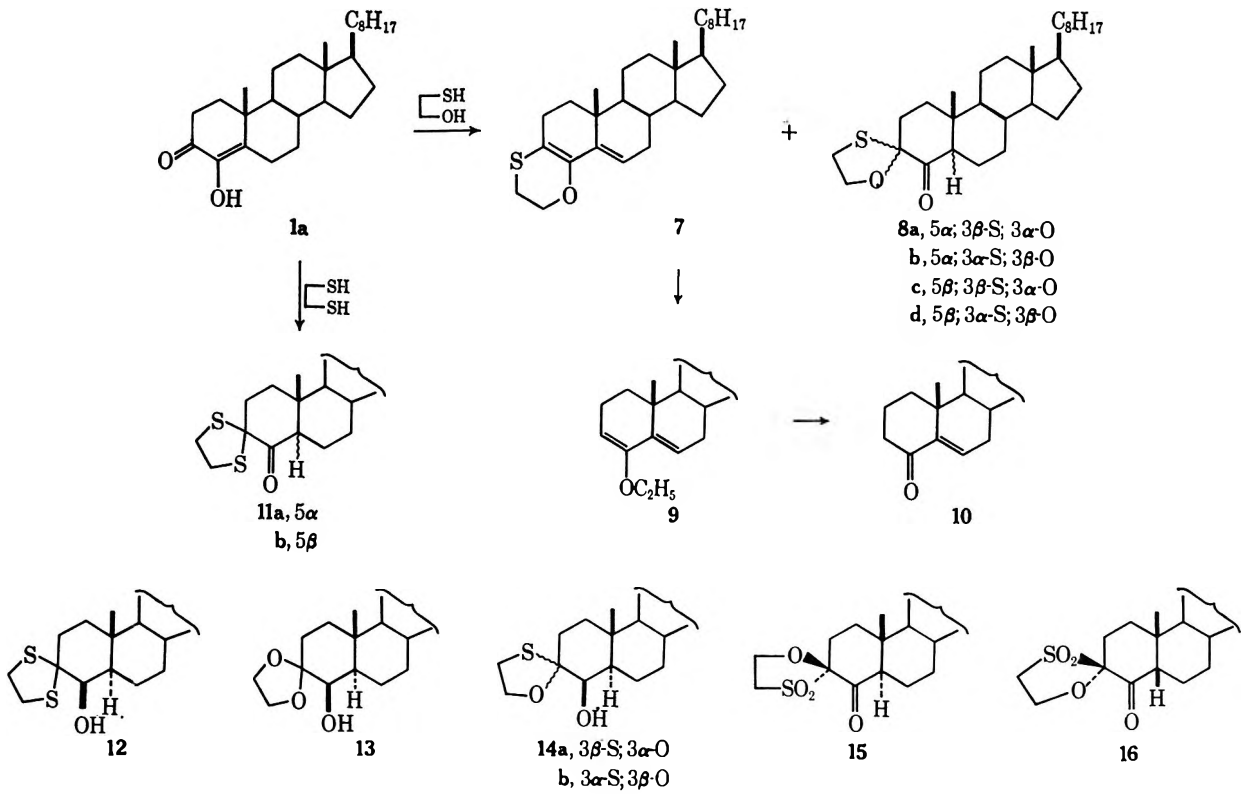
(16) Compare the C-19 methyl resonance for 5α-cholestan-4β-ol (δ 1.04, this paper) with that for 5α-cholestan-4α-ol (δ 0.78) recorded by D. Lavie, S. Greenfield, Y. Kashman, and E. Glotter, *Israel J. Chem.*, **5**, 151 (1967).

(17) Note also the data for the C-19 methyl resonance of 5α-androstan-4β-ol (δ 1.04) *vs.* that for 5α-androstan-4α-ol (δ 0.80), cited in the extensive nmr tabulations of J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, E. R. H. Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards, and P. D. Woodgate, *J. Chem. Soc. C*, 250 (1970).

(18) N. L. Allinger, M. A. Darooge, and R. B. Hermann, *J. Org. Chem.*, **26**, 3626 (1961).

(19) D. Lavie, cited in J. E. Bridgeman, P. C. Cherry, E. R. H. Jones, P. W. Lequesne, and G. D. Meakins, *Chem. Commun.*, 561 (1966).

SCHEME IV



be preference for the equatorial orientation of sulfur over oxygen by about 0.2 kcal/mol.[20] This view is supported by the report[21] that equilibration of the propylene moncthioketals of 4-*tert*-butylcyclohexanone with boron trifluoride as catalyst generates 55% of the isomer with sulfur equatorial.

On the other hand, equilibrations of the ethylene monothioketals of 4-*tert*-butylcyclohexanone, 3-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, and 3-*tert*-butylcyclohexanone, using boron trifluoride as catalyst, gave[22,23] mixtures favoring, in varying degree, the isomer with equatorial oxygen in each case. However, it was found[22] that equilibrium shifts occurred when the amount of boron trifluoride was varied in the case of 4-*tert*-butylcyclohexanone ethylene monothioketal, suggesting that a complexed intermediate might be involved. More recent work[20] on the boron trifluoride catalyzed equilibration of the ethylene monothioketals of 3,3,5-trimethylcyclohexanone strongly suggests that no significant complexing of catalyst with ketal occurs, in this case at least.

Our equilibration results with the ethylene monothioketals **8a–d** are consistent with equatorial preference for oxygen, and the problem of possible catalyst–ketal complex formation involved in the boron trifluoride equilibrations is, of course, not encountered in these base-catalyzed epimerizations at C-5. The conformational preference of oxygen for the equatorial orientation in these ketals is sufficient to invert the normal stability order of 4-oxo steroids [preponderantly 5α (A/B trans) at equilibrium] giving preponderantly the 5β isomer (A/B cis) in the case of the 3(*S*) isomers **8a** and **8c**.

However, dipole interactions[24] between C-3 equatorial oxygen (or sulfur) and the C-4 carbonyl group are undoubtedly also involved, thus complicating the situation, and further analysis at this time would be quite speculative. Our experiments can, however, be said to provide independent confirmation for the conformational preference of sulfur for the equatorial orientation in cyclohexyl ethylene monothioketals.

In conclusion, we note that monitoring by tlc of the reactions of ethylene glycol, 2-mercaptoethanol, and 1,2-ethanedithiol with the diosphenol **1a** showed that, in each case, 5β-4-oxo 3-ketals predominated initially over the 5α isomers and that acid-catalyzed equilibration at C-5 ensued. In the case of the 2-mercaptoethanol reaction, it was also shown that the [4,3-*b*]oxathiane **7** did not generate the ketals **8a–d** when put back into the ketalizing conditions, nor did the ketals generate discernable quantities of the oxathiane **7** under the reaction conditions.

Experimental Section[25]

3,5-Cholestadieno[3,4-*b*]dioxane (3a) and the Cholestane-3,4-dione 3-Ethylenedioxy Ketals (2a and 2b) from 4-Hydroxy-4-

(20) See M. P. Mertes, H. K. Lee, and R. L. Schowen, *J. Org. Chem.*, **34**, 2080 (1969), and references cited therein for a recent account of this situation.

(21) E. L. Eliel, E. W. Della, and M. Rogic, *ibid.*, **30**, 855 (1965).

(22) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962).

(23) M. P. Mertes, *J. Org. Chem.*, **28**, 2320 (1963).

(24) After completion of the spectroscopically based assignments of configuration to compounds **8a–d**, A. Cooper and D. A. Norton [*ibid.*, **33**, 3537 (1968)] carried out an X-ray crystal structure determination on compound **8b**. Their results, which conclusively confirm the structures of **8b** and hence of the other three isomeric monothioketals, show some distortion of the steroid A ring, probably due (at least in part) to dipole interaction between the equatorial oxygen substituent at C-3 and the C-4 carbonyl group.

(25) Melting points were determined on the Kofler hot stage. Optical rotations were measured in chloroform solution, as were infrared spectra, unless otherwise specified. Ultraviolet spectra were recorded using heptane or methanol solutions as noted, and nmr spectra refer to deuteriochloroform solutions with tetramethylsilane as internal reference. The silica gel used for column chromatography was Davison Chemical Co. Grade 923. Preparative thin layer chromatography (tlc) was carried out with 1.0-mm-thick layers of silica gel GF_{254}. Petroleum ether refers to the fraction boiling between 40 and 60°.

cholesten-3-one (1a).—A solution of the diosphenol **1a** (500 mg) in benzene (25 ml) and ethylene glycol (2 ml) together with *p*-toluenesulfonic acid (60 mg) was heated to reflux under a Dean-Stark water separator for 24 hr. The reaction mixture was cooled, washed successively with 10% aqueous sodium carbonate and water, dried (anhydrous solid Na_2CO_3), and evaporated *in vacuo* to give an oil. Chromatography on a Florisil column and elution with petroleum ether (bp 30–60°) gave 3,5-cholestadieno-[3,4-*b*]dioxane (**3a**, 170 mg): mp 77–78° (from methanol containing a trace of pyridine); $[\alpha]D$ −21°; λ_{max}^{MeOH} 258 nm (ϵ 15,200), shoulders at 250 (13,800) and 267 (10,800); ν_{max} 1631, 1668 cm^{-1}; nmr δ 0.70 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 4.08 (s, 4 H, OCH_2CH_2O), and 5.65 (s, 1 H, C=CH).

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.36; H, 11.20.

The Florisil column was then eluted with petroleum ether–ethyl acetate (4:1), and the mixture thereby obtained was separated by preparative tlc (petroleum ether–ethyl acetate, 19:1). This separation gave pure 5β-cholestane-3,4-dione 3-ethylenedioxy ketal (**2b**, 50 mg): mp 121–123° (from methanol); $\nu_{max}^{CCl_4}$ 1725 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 1.10 (s, 3 H, 19-CH_3), 2.55 (unresolved, 1 H, $W_{1/2}$ = 6.5 Hz, C-5 H), and 3.98 (m, 4 H, OCH_2CH_2O); mass spectrum 444 (M^+), 99 (base peak).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.56; H, 10.74.

There was also isolated the isomeric 5α-cholestane-3,4-dione 3-ethylenedioxy ketal (**2a**, 70 mg) which had mp 131–135° (from methanol). This material was not analytically pure, and the analytical sample was obtained as described in the two experiments immediately below.

4β-Hydroxy-5α-Cholestan-3-one 3-Ethylenedioxy Ketal (13).—To a stirred solution of the 4-oxo 3-ethylenedioxy ketal **2a** (150 mg) in ether (5 ml) was added lithium aluminum hydride (75 mg) in ether (5 ml) at room temperature. After 1.75 hr water was added and the mixture was extracted with chloroform. The chloroform extract was washed with saturated sodium chloride solution and then with water, then dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by preparative tlc (petroleum ether–ethyl acetate, 9:1) to give the analytically pure 4β-ol **13** (100 mg): mp 167–168° (from methylene chloride–acetone); $[\alpha]D$ +28°; $\nu_{max}^{CCl_4}$ 3592 cm^{-1}; nmr δ 0.66 (s, 3 H, 18-CH_3), 1.04 (s, 3 H, 19-CH_3), 3.38 (s, 1 H, $W_{1/2}$ = 4 Hz, CHOH), and 3.98 (s, 4 H, OCH_2CH_2O); mass spectrum 446 (M^+), 428, 99 (base peak).

Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.30; H, 11.45.

5α-Cholestane-3,4-dione 3-Ethylene Ketal (2a) from 4β-Hydroxy-5α-cholestan-3-one 3-Ethylene Ketal (13).—A solution of the 4β-ol **13** (80 mg) in acetone (25 ml) was oxidized with Jones reagent[26] in the usual way. The crude product was crystallized from methanol giving the pure 4-oxo compound **2a** (32 mg): mp 136–138°; $\nu_{max}^{CCl_4}$ 1731 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 0.72 (s, 3 H, 19-CH_3), 2.51 (q, 1 H, C-5 H, J_{aa} = 10 Hz, J_{ae} = 4 Hz); mass spectrum 444 (M^+), 99 (base peak).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 77.98; H, 10.68.

Cholesta-3,5-dieno[3,4-*b*]dioxane (3a) from 4-Acetoxy-4-cholesten-3-one (1b).—A mixture of 4-acetoxy-4-cholesten-3-one (**1b**, 400 mg), ethylene glycol (2 ml), benzene (40 ml), and *p*-toluenesulfonic acid (200 mg) was heated to reflux under a Dean-Stark water separator for 24 hr. The reaction mixture was cooled, washed successively with 10% aqueous sodium carbonate and water, dried (solid Na_2SO_4), and evaporated *in vacuo* to give an oil. Chromatography on Florisil and elution with benzene gave pure **3a** (128 mg), mp 77–78° (from methanol containing a trace of pyridine), identical in all respects with the same compound prepared from 4-hydroxy-4-cholesten-3-one (**1a**) as described above.

17β-Hydroxy-3,5-androstadieno[3,4-*b*]dioxane (3c).—A mixture of 4β,5β-oxido-17β-hydroxyandrostan-3-one (**4**, 4.1 g), ethylene glycol (5.0 ml), benzene (100 ml), and *p*-toluenesulfonic acid (220 mg) was heated to reflux under a Dean-Stark water separator for 22 hr. The reaction mixture was worked up exactly as for the other ethylene glycol reactions described above, and the crude product was chromatographed on Florisil. Elution with benzene gave crude **3c**, which was crystallized from methanol containing a trace of pyridine to give pure **3c** (1.67 g): mp 150–175°; $[\alpha]D$ −42°; λ_{max}^{MeOH} 258 nm (13,300), shoulders at 250 (12,000) and 268 (9200); ν_{max} 1632, 1669 cm^{-1}; nmr δ 0.78 (s, 3 H, 18-CH_3), 1.03 (s, 3 H, 19-CH_3), 4.09 (s, 4 H, OCH_2-CH_2O), and 5.67 (s, 1 H, >C=CH).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.21; H, 9.15.

17β-Propionoxy-3,5-androstadieno[3,4-*b*]dioxane (3b). A. From 17β-Hydroxy-3,5-androstadieno[3,4-*b*]dioxane (3c).—A solution of **3c** (300 mg) in pyridine and propionic anhydride (14 ml, 1:1 mixture) was left for 5 hr at 25°. Water was added, the mixture was filtered, and the solid residue was washed with water, dried, and chromatographed on Florisil. Elution with benzene gave a solid, which was crystallized from methanol to give pure 17β-propionate (**3b**, 100 mg) identical in all respects with material obtained as described in B below.

B. From 17β-Propionoxy-4-hydroxy-4-androsten-3-one (1c).—A solution of **1c** (3.0 g) and *p*-toluenesulfonic acid (100 mg) in 2-methyl-2-ethyl-1,3-dioxolane (100 ml) was distilled slowly through a Vigreux column for 4 hr. Additional amounts of 2-methyl-2-ethyl-1,3-dioxolane (50 ml) and *p*-toluenesulfonic acid (100 mg) were added and the mixture was heated under reflux for 24 hr. The reaction mixture was cooled, and benzene and 10% aqueous sodium carbonate (10 ml) were added. The benzene layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography of the crude product on Florisil gave, on elution with benzene, pure **3b** (400 mg). Crystallization from methanol gave analytically pure **3b** (180 mg): mp 157–174°; λ_{max}^{MeOH} 258 nm (13,400), shoulders at 250 (12,900) and 267 (11,700); ν_{max} 1632, 1669 cm^{-1}; nmr δ 0.83 (s, 3 H, 18-CH_3), 1.03 (s, 3 H, 19-CH_3), 4.09 (s, 4 H, OCH_2-CH_2O), and 5.67 (s, 1 H, <C=CH); mass spectrum 386 (M^+), 358.

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.51; H, 8.90.

Reaction of 4-Hydroxy-4-cholesten-3-one (1a) with 2-Mercaptoethanol. A. In Benzene at Reflux.—To a solution of the diosphenol **1a** (5.0 g) in benzene (100 ml) and 2-mercaptoethanol (10 ml) was added *p*-toluenesulfonic acid (1.0 g) and the mixture was heated to reflux under a Dean-Stark water separator for 5 min. The reaction mixture was cooled and neutralized with 10% aqueous sodium carbonate solution, and the benzene layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was dissolved in petroleum ether and chromatographed on Florisil. Elution with petroleum ether gave 3,5-cholestadieno[4,3-*b*]oxathiane (**7**, 484 mg): mp 130–132° (from methanol); $[\alpha]D$ −91°; λ_{max} 279 nm (13,000), 221 (8800); $\nu_{max}^{CCl_4}$ 1610 cm^{-1}; nmr δ 0.70 (s, 3 H, 18-CH_3), 0.99 (s, 3 H, 19-CH_3), 3.02 (m, 2 H, SCH_2), 4.27 (m, 2 H, OCH_2), and 5.86 (s, 1 H, C-6 vinyl H); mass spectrum 442 (M^+), 427 ($M - CH_3$).

Anal. Calcd for $C_{29}H_{46}OS$: C, 78.68; H, 10.47; S, 7.23. Found: C, 78.32; H, 10.19; S, 7.55.

Further elution with petroleum ether gave 5β-cholestane-3,4-dione 3-ethylene monothioketal 3(*S*) isomer (**8c**, 318 mg): mp 125–125.5° (from methanol); ν_{max} 1717 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 1.09 (s, 3 H, 19-CH_3), 2.58 (m, 1 H, 5β H), 2.99 (t, J = 6 Hz, 2 H, SCH_2), and 4.28 (m, 2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50; S, 6.94. Found: C, 75.54; H, 10.37; S, 7.16.

Further elution with petroleum ether gave mixtures, from which were separated by preparative tlc (petroleum ether–ethyl acetate, 19:1) the following two compounds. 5β-cholestane-3,4-dione 3-ethylene monothioketal 3(*R*) isomer (**8d**, 21 mg): mp 119–120° (from methanol); ν_{max}^{CCl} 1720 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 1.09 (s, 3 H, 19-CH_3), 2.68 (m, 1 H, 5β H), 3.02 (m, 2 H, SCH_2), and 2 multiplets centered on 3.68 and 4.17 (2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50. Found: C, 75.15; H, 10.21.

5α-cholestane-3,4-dione 3-ethylene monothioketal 3(*S*) isomer (**8a**, 14 mg): mp 139–140° (from methanol); $\nu_{max}^{CCl_4}$ 1726 cm^{-1}; nmr δ 0.64 (s, 3 H, 18-CH_3), 0.72 (s, 3 H, 19-CH_3) 3.00 (m, 2 H, SCH_2), and 4.19 (m, 2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50; S, 6.94. Found: C, 75.67; H, 10.64; S, 7.04.

Further elution of the Florisil column with chloroform gave 5α-cholestane-3,4-dione 3-ethylene monothioketal 3(*R*) isomer (**8b**, 827 mg): mp 148.5–150.5°; $\nu_{max}^{CCl_4}$ 1722 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 0.73 (s, 3 H, 19-CH_3), 3.00 (m, 2 H, SCH_2), and 4.20 (m, 2 H, OCH_2).

(26) R. G. Curtis, I. M. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

Anal. Calcd for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50; S, 6.94. Found: C, 75.55; H, 10.35; S, 7.19.

B. In Benzene at 60°.—To a solution of the diosphenol **1a** (5.0 g) in benzene (750 ml) and 2-mercaptoethanol (50 ml) was added *p*-toluenesulfonic acid (1.0 g) and the mixture was stirred magnetically at 60° for 2 hr. The reaction mixture was worked up exactly as in A above, and the crude product was chromatographed on Florisil. Elution with petroleum ether gave, first, the [4,3-*b*]oxathiane **7** (458 mg) described above, mp 130–132°. Further elution with petroleum ether gave 28 mg of a new compound, possibly a cholestane-3,4-dione bis(ethylene monothioketal): mp 146–147° (from methanol); mass spectrum 520 (M^+), 460, 442.

Anal. Calcd for $C_{31}H_{52}O_2S_2$: C, 71.50; H, 10.07; S, 12.29. Found: C, 71.77; H, 10.28; S, 12.02.

The next petroleum ether fractions provided another new compound (80 mg), possibly another cholestane-3,4-dione bis(ethylene monothioketal): mp 163.5–165° (from methanol); mass spectrum 520 (M^+), 505, 492, 460.

Anal. Calcd for $C_{31}H_{52}O_2S_2$: C, 71.50; H, 10.07. Found: 72.49; H, 10.08.

Further elution with petroleum ether and petroleum ether–ethyl acetate mixtures gave three of the four isomeric cholestane-3,4-dione 3-ethylene monothioketals described in A above, in the following quantities as pure compounds after crystallization from methanol: 5β-cholestane-3,4-dione 3-ethylene monothioketal (**8c**), 348 mg; 5α-cholestane-3,4-dione 3-ethylene monothioketal (**8a**), 169 mg; 5α-cholestane-3,4-dione 3-ethylene monothioketal (**8b**), 893 mg.

Sulfone 15 Derived from 5α-Cholestane-3,4-dione 3-Ethylene Monothioketal (8b).—A solution of the monothioketal **8b** (265 mg) and *m*-chloroperbenzoic acid (625 mg) in chloroform (25 ml) was heated to reflux for 35 min. The solution was cooled, washed successively with 10% aqueous sodium sulfite, 10% aqueous sodium carbonate, and water, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was chromatographed on silica gel. Elution with chloroform–ethyl acetate (19:1) gave the sulfone **15** (240 mg) which was crystallized from methanol to give analytically pure **15** (193 mg): mp 191–193°; ν_{max} 1717, 1316, 1124 cm^{-1}; nmr δ 0.65 (s, 3 H, 18-CH_3), 0.78 (s, 3 H, 19-CH_3), 3.25 (m, 2 H, SO_2CH_2), and 4.51 (m, 2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_4S$: C, 70.69; H, 9.82; S, 6.49. Found: C, 70.65; H, 9.58; S, 6.36.

Sulfone 16 Derived from 5β-Cholestane-3,4-dione 3-Ethylene Monothioketal (8c).—A solution of the monothioketal **8c** (258 mg) and *m*-chloroperbenzoic acid (620 mg) in chloroform (25 ml) was heated to reflux for 35 min. The solution was cooled, washed successively with 10% aqueous sodium sulfite, 10% aqueous sodium carbonate, and water, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product (248 mg) was crystallized from methanol to give the analytically pure sulfone **16** (204 mg): mp 177–180°; ν_{max} 1712, 1315, 1110 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 1.13 (s, 3 H, 19-CH_3), 2.68 (m, 1 H, 5β H), 3.28 (m, 2 H, $SOCH_2$), and 4.60 (m, 2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_4S$: C, 70.69; H, 9.82; S, 6.49. Found: C, 70.76; H, 9.62; S, 6.41.

4-Ethoxy-3,5-cholestadiene (9).—3,5-Cholestadieno[4,3-*b*]oxathiane (**7**, 500 mg) was desulfurized by stirring with Raney nickel (2 teaspoons; W-2) in benzene (50 ml) for 75 min. The mixture was filtered and evaporated *in vacuo* and the residue was crystallized twice from ether–methanol, giving the enol ether **9** (150 mg): mp 71–75°; $[\alpha]_D$ −19°; $\lambda_{max}^{heptane}$ 243 nm (12,000); ν_{max} 1650, 1618 cm^{-1}; nmr δ 0.67 (s, 3, 18-CH_3), 0.94 (s, 3, 19-CH_3), 1.28 (t, 3 H, J = 7 Hz, CH_3 of ethoxyl group), 3.66 (q, 2 H, J = 7 Hz, CH_2 of ethoxy group), 4.64 (s, 1, C-3 vinyl hydrogen), and 6.02 (s, 1, C-6 vinyl hydrogen); mass spectrum 412 (M^+), 397.

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.24; H, 11.28.

5-Cholesten-4-one (10) from 4-Ethoxy-3,5-cholestadiene (9).—The enol ether **9** (110 mg) was dissolved in a mixture of ethanol (22 ml), water (2 ml), and glacial acetic acid (2 ml), and the solution was heated on the steam bath for 3 min and then left at 25° for 30 min. The reaction mixture was then concentrated to about 15 ml *in vacuo*, diluted with water, and extracted with chloroform. The chloroform extract was washed with water and evaporated *in vacuo* to an oily residue which was chromatographed on silica gel (6 g). Elution with petroleum ether–ethyl acetate (19:1) gave crystalline 5-cholesten-4-one (**10**, 80 mg): mp 112–114° (from methylene chloride–methanol); $[\alpha]_D$ −31° (lit.[8] mp 112°; $[\alpha]_D$ −32°).

5α- and 5β-Cholestane-3,4-dione 3-Ethylene Dithioketal (11a and 11b).—A mixture of 4-hydroxy-4-cholesten-3-one (**1a**, 500 mg), 1,2-ethanedithiol (1.0 ml), and benzene (40 ml) containing *p*-toluenesulfonic acid (110 mg) was heated to reflux under a Dean-Stark water separator for 20 min. The mixture was cooled, washed successively with 10% aqueous Na_2CO_3 solution and water, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was dissolved in petroleum ether and chromatographed on Florisil. Elution with petroleum ether gave the 5β-dithioketal (**11b**) which was recrystallized from methanol to give pure **11b** (70 mg): mp 131.5–132°; $[\alpha]_D$ +109° (lit.[12] mp 128°, $[\alpha]_D$ +126°); $\nu_{max}^{CCl_4}$ 1712 cm^{-1}; nmr δ 0.64 (s, 3 H, 18-CH_3), 1.09 (s, 3 H, 19-CH_3), and 3.29 (m, 4 H, SCH_2CH_2S).

Anal. Calcd for $C_{29}H_{48}OS_2$: C, 73.07; H, 10.15; S, 13.42. Found: C, 73.36; H, 10.26; S, 13.28.

Further elution with petroleum ether–ethyl acetate (19:1) gave the 5α-dithioketal **11a** which was crystallized from methanol to give the analytical sample (60 mg): mp 143–144°; $[\alpha]_D$ 0°; $\nu_{max}^{CCl_4}$ 1716 cm^{-1}; nmr δ 0.65 (s, 3 H, 18-CH_3) 0.73 (s, 3 H, 19-CH_3), and 3.27 (s, 4 H, SCH_2CH_2S).

Anal. Calcd for $C_{29}H_{48}OS_2$: C, 73.07; H, 10.15; S, 13.42. Found: C, 73.53; H, 10.33; S, 13.25.

4β-Hydroxy-5α-Cholestan-3-one 3-Ethylene Dithioketal (12).—To a solution of the 4-oxo compound **11a** (300 mg) in dioxane (54 ml) and water (6 ml) was added sodium borohydride (300 mg), and the solution was stirred at room temperature for 72 hr. The crude product (isolated by precipitation with water and filtration) was purified by preparative tlc (petroleum ether–ethyl acetate, 9:1) to give the analytically pure 4β-hydroxy compound **12** (202 mg): mp 174–175° (from methylene chloride–methanol); $[\alpha]_D$ +24°; $\nu_{max}^{CCl_4}$ 3453 cm^{-1}; nmr δ 0.65 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 3.27 (s, H, SCH_2CH_2S), and 3.50 (s, 1 H, $W_{1/2}$ = 2.5 Hz, CHOH); mass spectrum 478 (M^+), 460.

Anal. Calcd for $C_{29}H_{50}OS_2$: C, 72.76; H, 10.53; S, 13.37. Found: C, 72.82; H, 10.84; S, 13.09.

In addition, a minor product (9 mg) was isolated from the preparative tlc. This compound had mp 176–177° (from methanol), mass spectrum 478 (M^+), 460, and is tentatively formulated as 5α-cholestan-4α-ol-3-one 3-ethylene dithioketal. Lack of material precluded further characterization.

5α-Cholestan-4β-ol from 4β-Hydroxy-5α-cholestan-3-one 3-Ethylene Dithioketal (12).—The 4β-hydroxy compound **12** (65 mg) was desulfurized by treatment with W-2 Raney nickel in ethanol under reflux for 1.5 hr. Preparative tlc (petroleum ether–ethyl acetate, 9:1) of the crude product gave 5α-cholestan-4β-ol (20 mg), mp 135–136° (from methanol), identical with an authentic specimen as judged by tlc, melting point, and infrared comparison. In addition, there was isolated from the preparative tlc plate 19 mg of pure 5α-cholestan-4-one, identified by tlc, melting point, and infrared comparison.

4β-Hydroxy-5α-cholestan-3-one 3-Ethylene Monothioketal [14b, 3(*R*) Isomer].—To a solution of the 4-ketone **8b** (200 mg) in dioxane (36 ml) was added sodium borohydride (200 mg) in water (4 ml) and the mixture was left at 25° for 66 hr. The crude product (obtained by dilution of the reaction mixture with water and extraction with chloroform) was purified by preparative tlc (petroleum ether–ethyl acetate, 9:1). The analytically pure 4β-hydroxy steroid **14b** (112 mg) had mp 157–158° (from methanol); $[\alpha]_D$ +26°; $\nu_{max}^{CCl_4}$ 3593 cm^{-1}; nmr spectrum δ 0.62 (s, 3 H, 18-CH_3), 1.01 (s, 3 H, 19-CH_3), 2.94 (t, J = 5.5 Hz, 2 H, SCH_2), 3.58 (s, $W_{1/2}$ = 3 Hz, 1 H, CHOH), and 4.02 (m, 2 H, OCH_2); mass spectrum 462 (M^+), 444, 115 (base peak).

Anal. Calcd for $C_{29}H_{50}O_2S$: C, 75.28; H, 10.89; S, 6.92. Found: C, 75.29; H, 10.60; S, 6.82.

4β-Hydroxy-5α-cholestan-3-one 3-Ethylene Monothioketal [14a, 3(*S*) Isomer].—A solution of the 4-oxo compound **8a** (140 mg) in dioxane (25 ml) and water (2.8 ml) was treated with sodium borohydride (140 mg) and left at room temperature for 48 hr. The crude product was purified by preparative tlc (petroleum ether–ethyl acetate, 9:1), and the analytically pure **14a** (73 mg) had mp 160–161° (from methylene chloride–methanol); $\nu_{max}^{CCl_4}$ 3572 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 0.98 (s, 3 H, 19-CH_3), 2.92 (t, J = 5.5 Hz, 2 H, SCH_2), 3.30 (s, $W_{1/2}$ = 5 Hz, 1 H, CHOH), and 4.08 (t, J = 5.5 Hz, 2 H, OCH_2); mass spectrum 462 (M^+), 444, 115 (base peak).

Anal. Calcd for $C_{29}H_{50}O_2S$: C, 75.28; H, 10.89; S, 6.92. Found: C, 74.88; H, 10.95; S, 7.16.

Equilibration of 5β-Cholestan-4-one Using Methanolic Potassium Hydroxide.—A solution of 5β-cholestan-4-one (66 mg) in 10% methanolic potassium hydroxide solution was heated to reflux for 18 hr. The crude product was isolated by extraction with ether (3 times), and evaporation of the ethereal extract after washing with water and drying (Na_2SO_4). Preparative tlc (petroleum ether–ethyl acetate, 9:1) gave pure 5α-cholestan-4-one (53 mg) and pure 5β-cholestan-4-one (11 mg), by elution of the scraped out zones with ethyl acetate. The products were identified by tlc, infrared comparison, and melting point, and mixture melting point determination.

Equilibration of Cholestan-4-one 3-Ethylene Monothioketals 8b and 8d with Potassium Hydroxide in Methanol. A.—The 5α-cholestan-4-one derivative **8b** (10 mg) was dissolved in 10% methanolic potassium hydroxide solution (5 ml) and the solution was heated under reflux for 4 hr. Monitoring of the reaction solution by tlc (petroleum ether–ethyl acetate, 19:1) showed no change, and the reaction mixture was worked up by dilution with water, extraction with ether, and evaporation of the dried (Na_2SO_4) ethereal extract. The crude residue (9.3 mg) was unchanged **8b** as shown by tlc, infrared comparison, and melting point, and mixture melting point determination.

B.—The 5β-cholestan-4-one derivative **8d** (6 mg) was dissolved in 10% methanolic potassium hydroxide solution (4 ml) and the solution was heated under reflux. Monitoring of the reaction solution by tlc (petroleum ether–ethyl acetate, 19:1) showed that no **8d** was present after 2 hr, but that a new compound was present with an R_F identical with that of the 5α compound **8b**. After 3 hr the situation was unchanged, and work-up of the reaction mixture as for A above gave crude product (5.5 mg) which proved identical with compound **8b** as shown by tlc, infrared comparison, and melting point, and mixture melting point determination.

Equilibration of Cholestan-4-one 3-Ethylene Monothioketals 8a and 8c with Potassium Hydroxide in Methanol. A.—A solution of the 3-monothioketal **8a** (9 mg) in 10% methanolic potassium hydroxide solution (5 ml) was heated under reflux for 2.5 hr. Monitoring of the reaction solution by tlc (petroleum ether–ethyl acetate, 19:1) had shown that no further change occurred after 2-hr reflux. Work-up as for the previous equilibration and preparative tlc of the crude product (8 mg) gave pure starting material **8a** (1.0 mg) and pure compound **8c** (6.0 mg), identified in the former case by tlc, melting point, and mixture melting point determination, and in the latter case by the above criteria and also by infrared comparison.

B.—A solution of the 3-monothioketal (**8c**, 100 mg) in 10% methanolic potassium hydroxide solution (50 ml) was heated under reflux for 2.5 hr. Work-up as for the previous equilibrations gave crude product (95 mg) which was separated by preparative tlc into pure starting material **8c** (78 mg) and pure compound **8a** (12 mg). Identification in each case was by tlc, infrared comparison, melting point, and mixture melting point determination.

Registry No.—**2a**, 18897-72-8; **2b**, 18897-73-9; **3a**, 28876-03-1; **3b**, 28876-04-2; **3c**, 28876-05-3; **7**, 28876-06-4; **8a**, 18897-78-4; **8b**, 17021-85-1; **8c**, 18897-79-5; **8d**, 18897-77-3; **9**, 28856-58-8; **11a**, 18897-74-0; **11b**, 18897-75-1; **12**, 28856-61-3; **13**, 28856-62-4; **14a**, 18897-83-1; **14b**, 18897-82-0; **15**, 18897-80-8; **16**, 18897-81-9; 5α-cholestan-4β-ol, 566-50-7; cholestane-3,4-dione bis(ethylene monothioketal), 28856-67-9.

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β-Carbonylamides in Peptide Chemistry. Synthesis of Optically Active Peptides from *N*-Acetoacetylamino Acids *via* 2-Acetonylidenoxazolidin-5-ones[1]

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N-Acetoacetylamino acids react with dicyclohexylcarbodiimide yielding 2-acetonylidenoxazolidin-5-ones. These condense in turn with nucleophiles producing amides and peptides with retention of configuration.

In contrast to the widespread tendency of activated *N*-acylamino acids to racemize under conditions suitable for peptide synthesis,[2] we recently found that *N*-acetoacetylamino acids (AcA-aa) (**1**) yield optically pure peptide derivatives under certain conditions;[3] furthermore, the acetoacetyl protecting group can be selectively cleaved with hydroxylamine under very mild conditions.[3,4]

To explore the reasons for this retention of configuration, we examined the behavior of some AcA-aa when treated with dicyclohexylcarbodiimide (DCCI) and isolated reactive acylating agents that we regard as 2-acetonylidenoxazolidin-5-ones. Their optical stability and tendency to condense with nucleophiles have been compared with similar properties of some related azlactones (**2**).

Representative *N*-AcA-aa (**1**) were reacted with DCCI under the conditions used in peptide synthesis but omitting a nucleophilic partner. A molar amount of dicyclohexylurea (DCU) was formed, while the optical activities of the solutions shifted to higher positive values. Prompt lyophylization of the solutions yielded solid, frequently crystalline products.

The uv spectra exhibited a strongly conjugated chromophore [$\lambda_{max}^{dioxane}$ near 285 nm (ϵ *ca.* 10,000)] ruling out the formation of anhydrides;[5] in the ir spectra, a strong absorption at 1835–1840 cm^{-1} accounted for the presence of a carbonyl group in a strained lactone ring. Finally, the nmr spectra showed absorptions that could more satisfactorily be ascribed to 2-acetonylidenoxazolidin-5-ones (**3**) than to 2-acetonyl-2-oxazolin-5-ones (**2′** and possible tautomers **2″**, **2‴**), as might be expected since β-aminoenones are more stable than the isomeric β-imino ketones.[6] Furthermore, evidence has been obtained that β-aminoenones

(1) *Cf.* C. Di Bello, F. Filira, and F. D'Angeli, "Peptides 1969," E. Scoffone, Ed., North-Holland, Amsterdam, 1969, p 35.

(2) G. T. Young, "Peptides 1967," H. C. Beyerman, *et al.*, Ed., North-Holland, Amsterdam, 1967, p 55.

(3) C. Di Bello, F. Filira, V. Giormani, and F. D'Angeli, *J. Chem. Soc. C*, 350 (1969), and references cited therein.

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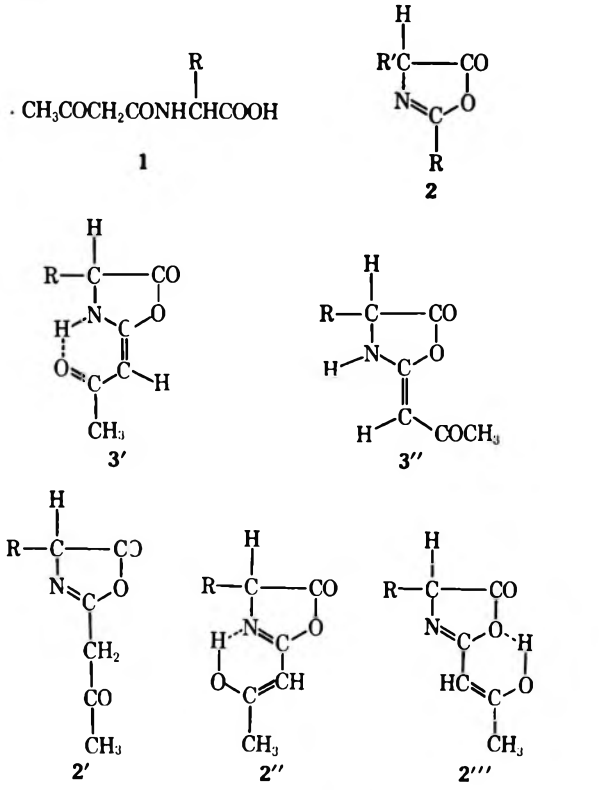
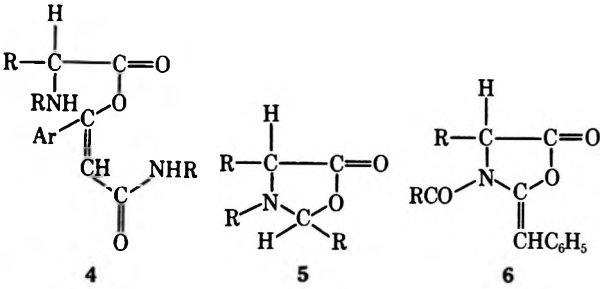
are formed also from *N*-methyl AcA-aa.[7a] However, the nmr spectra of the present compounds display signals of only one vinyl proton, instead of two as required if both stereoisomers **3′** and **3″** were present.[7b] The single isomer suggested by this feature should be **3′** which can be stabilized by intramolecular hydrogen bonding.



The 2-acetonylidenoxazolidin-5-ones **3a–d** were optically stable for at least a few days when stored dry at room temperature in the solid state after lyophylization. In dioxane solution at 20°, the loss of optical activity was faster and some influence of the substituent at C_4 was observed; no conclusions regarding relative optical stabilities can be drawn at present. When the optically active 2-acetonylidenoxazolidin-5-ones were reacted with nucleophiles, optically pure condensation products were obtained, as demonstrated by independent synthesis or glpc analysis.

Qualitative rate experiments showed that a 2-acetonylidenoxazolidin-5-one (**3**) condenses with aniline, valine methyl ester, or benzylamine somewhat faster than an azlactone (**2**). It is known, on the other hand, that azlactones racemize at a faster rate than they condense with nucleophiles.[8]

The similarity of compounds **3a–d** to Woodward's enol esters **4**[9] as well as to N-substituted oxazolidin-5-ones **5** and *N*-acyl-2-benzylidenoxazolidin-5-ones **6** should be pointed out.[10] All have acylating properties, and compounds of type **4** and **5** were shown to yield optically active peptides and amides.[9,11]



Whether 2-alkylidenoxazolidin-5-ones (**3**) indeed play a role as intermediates in the condensation of AcA-aa with nucleophiles by means of DCCI has not yet been established. The observed retention of configuration may be due to quenching of the path involving oxazolin-5-ones (**2**), whose intermediacy may seriously affect the optical purity in the condensation step. Further studies on structural features and possible applications of 2-acetonylidenoxazolidin-5-ones (**3**) are in progress.

Experimental Section[12,13]

Acetoacetylamino Acids.—The following acids were used: AcA-L-Ala-OH, mp 92–93°, $[\alpha]$ −4.6°, λ_{max} 245 nm (ϵ 3830); AcA-L-Val-OH, mp 124–125°, $[\alpha]$ +7.4°, λ_{max} 245 nm (ϵ 2060); AcA-L-Leu-OH, mp 124–125°, $[\alpha]$ −16.3°; λ_{max} 245 nm (ϵ 2100);[3] AcA-L-Phe-OH, mp 109–110°, $[\alpha]$ +68.2°, λ_{max} 245 nm (ϵ 2340), prisms from ethyl acetate–petroleum ether (bp 30–60°). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.6. Found: C, 63.35; H, 6.06; N, 5.8.

Optically Active Azlactones (2). 2-Phenyl-4-isobutyl-2-oxazolin-5-one (2a).—A solution of *N*-benzoyl-L-leucine[14a] (1.125 g, 0.005 mol) in 10 ml of anhydrous dioxane, mixed with DCCI (1.03 g, 0.005 mol) and allowed to stand 2 hr, gave 98% DCU. A sample of the solution, diluted with dioxane to a 2% concentration, gave $[\alpha]$ −63.8°. Lyophilization yielded colorless prisms (0.85 g, 75%): mp 51–52°; ir 1830 (s, CO), 1660 (s, C=N), 1580 cm^{-1} (w). *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.17; H, 7.25; N, 6.56.

The racemic product (mp 56–57°) had been previously obtained from *N*-benzoyl-DL-leucine.[14b,15]

2-Phenyl-4-isopropyl-2-oxazolin-5-one (2b) was obtained from *N*-benzoyl-L-valine[16a] in the same manner as the above compound: ir 1830 cm^{-1} (s, CO); $[\alpha]$ −77.8°.[16b]

2-Acetonyliden-4-methyloxazolidin-5-one (3a) and Analogous Products (3b–d). A.—A sample of AcA-L-alanine (0.45 g, 0.0026 mol) was dissolved in 5 ml of anhydrous dioxane and mixed with DCCI (0.53 g, 0.0026 mol). After 2 hr at room temperature, precipitation of DCU was complete; it was filtered off; and the solution was chilled, lyophilized, and dried over P_2O_5 (0.394 g, 98%). The product was a colorless microcrystalline solid: mp 113–116°; $[\alpha]$ +49.5°; λ_{max} 284 nm (ϵ 13,000); ir 3280

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(12) Optical activities were measured with a Perkin-Elmer 141 polarimeter; maximum values observed are reported as $[\alpha]^{25}D$ for 2% solutions in dioxane, if not otherwise stated. Melting points were taken in a Kofler apparatus. Spectra were measured as follows: ir, Perkin-Elmer Model 337 double beam recording spectrophotometer equipped with sodium chloride optics (in CCl_4); uv, Coleman Hitachi 124 double beam recording spectrophotometer (in dioxane); nmr, Perkin-Elmer R12 spectrometer (in $CDCl_3$). For thin layer chromatography (tlc), precoated plates of silica gel Merck F 254 were used, with ethyl acetate–benzene (2:1) as eluent. We acknowledge the skillful technical assistance of Mr. Adriano Mencini.

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(15) J. W. Cornforth, "The Chemistry of Penicillin," Princeton University Press, 1949, p 775.

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(NH), 1840 (s, ring CO), 1720 (w), 1670 (s, conjd CO), 1620 (w), 1470 cm^{-1}; nmr δ 8.8 (NH), 5.2 (=CH), 4.3 (C_4H), 2.1 ($COCH_3$) 1.5 (d, C_4 CH_3). *Anal.* Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.07. Found: C, 54.52; H, 6.33; N, 9.33.

Compounds **3b–d**, prepared from AcA-L-valine, -L-leucine, and -L-phenylalanine, had analogous properties, minor differences being those expected for the group at C_4. The samples, dried to constant weight and not recrystallized, were colorless microcrystalline solids that could be stored for days in a drybox with no change; yields were almost quantitative. The nmr spectra indicated minor contamination by the parent AcA-aa.

3b [R = $CH(CH_3)_2$]: mp 80–85°; [α] +70°; λ_{max} 283 nm (ϵ 11,500). *Anal.* Calcd for $C_9H_{13}NO_3$: C, 59.01; H, 7.15; N, 7.64. Found: C, 58.99; H, 7.13; N, 7.71.

3c [R = $CH_2CH(CH_3)_2$]: mp 107–109°; [α] +63.5°; λ_{max} 284 nm (ϵ 11,000). *Anal.* Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.87; H, 7.56; N, 7.35.

3d (R = $CH_2C_6H_5$): mp 130–133°; [α] +92°; λ_{max} 285 nm (ϵ 12,500). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.57; H, 5.67; N, 6.06. Found: C, 67.43; H, 5.50; N, 6.01.

B.—Similar reactions were carried out in anhydrous tetrahydrofuran, dichloromethane, ether, or dioxane. After filtration of the DCU, the solutions were promptly diluted to standard volumes. Uv and ir spectra and specific rotations were in most cases identical with those of the above crystalline products.

The nmr spectrum of a reaction mixture obtained from AcA-L-Val-OH in $CDCl_3$, after only 45 min incubation with 2 mol of DCCI and filtration of DCU, showed again a single vinyl peak (δ 5.1).

Samples of 2% dioxane solutions were stored at room temperature and the decrease of optical activity with time was followed. Whereas in some cases (compounds **3a** and **3b**) only ~20% optical activity was lost in 10 days, in others (compounds **3c** and **3d**) more than 50% was lost within 2 days, as was the case for the two azlactones (**2a,b**) used as references.

***N*-Acetoacetyl-L-leucylglycine Ethyl Ester.**—A sample of AcA-L-leucine (1.075 g, 0.005 mol) in 10 ml of anhydrous dioxane was added with DCCI (1.03 g, 0.005 mol). After 2 hr the DCU was filtered and rapidly washed with a little dioxane; the solution and washings were mixed under stirring with a solution of free glycine ethyl ester[17] (0.515 g, 0.005 mol) in 5 ml of dioxane and allowed to stand overnight. Upon lyophilization and trituration with petroleum ether, a colorless solid was obtained (1.39 g, 92%). It was freed from contaminating DCU and AcA-leucine by column chromatography (SiO_2, ethyl acetate–benzene 2:1), yielding the pure title compound (1.26 g, 84%), mp 87–88°, [α] −47.5° (2%, ethanol). This sample was identical with the one obtained upon acetoacetylation of H-L-Leu-Gly-OEt, obtained in turn *via* Z.[3]

***N*-Acetoacetyl-L-valyl-L-valine Methyl Ester.**—A solution containing about 5 mmol of 2-acetonyliden-4-isopropyloxazolidin-5-one (**3b**) in 10 ml of dioxane, obtained from 0.005 mol each of AcA-L-valine and DCCI and freed from DCU, was treated with H-L-Val-OMe (5 mmol) in 15 ml of dioxane and left overnight. By working up the mixture as above, AcA-L-Val-L-valine was obtained (98%): mp 55–58°; [α] −53.2° (2%, ethanol); tlc R_f 0.34 ($FeCl_3$). A sample was deacetoacetylated and then trifluoroacetylated, yielding N-TFA-L-Val-L-Val-OMe.[3] Glpc[18a] showed contamination by no more than 1% of the DL isomer.

Acetoacetyl-L-leucine-*N*-benzylamide.—A solution containing about 10 mmol of 2-acetonyliden-4-isobutyloxazolidin-5-one (**3c**) in 20 ml of dioxane was obtained as described above from 10 mmol each of AcA-L-leucine and DCCI. After removal of DCU, the solution was treated with benzylamine (1.7 g, 0.01 mol), concentrated, and triturated with petroleum ether (2.7 g, 90%): colorless crystals; mp 112–113°; [α] −43.5° (2%, ethanol); R_f 0.5 (I_2NaN_3). *Anal.* Calcd for $C_{15}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.61; H, 8.15; N, 8.87.

A sample of the amide was deacetoacetylated with hydroxylamine[3] and reacted with benzyloxycarbonyl chloride. *Z*-Leucine benzylamide was obtained, identical with an authentic sample, mp 112–113°, [α] −17.2° (1.2%, ethanol).[18b]

Comparative Rate Experiments. Condensation of 2-Acetonylidenoxazolidin-5-ones and Oxazolin-5-one with Nucleophiles. A. Condensation with Aniline.—In a calibrated flask, a sample of 2-acetonyliden-4-isobutyloxazolidin-5-one (**3c**) (37.5 mg, 0.188 mmol) in 2–3 ml of dioxane was added with aniline (876 mg, 9.4 mmol) under stirring, and the volume was brought up to 5 ml (final concentrations, 0.0376 and 1.88 *M*, respectively). The drop of the concentration of **3c** was followed by reading this solution at 1840 cm^{-1}, using as a reference a solution of aniline of the same concentration (0.2-mm KBr cells). A straight line was obtained by plotting the logarithms of absorbances *vs.* time up to 1660 sec. The slope gave $K_{obsd} = 2.9 \times 10^{-4}$ corresponding to $t_{1/2}$ of 2375 sec.

A dioxane solution of 2-phenyl-4-isobutyl-2-oxazolin-5-one (**2a**) (41 mg, 0.188 mmol) and aniline, having the same concentration of the above experiment, was analyzed as described above at 1834 cm^{-1}. A straight line was obtained up to 5000 sec. K_{obsd} = 0.898×10^{-4} sec^{-1}; $t_{1/2}$, 7736 sec.

B. Condensation with Valine Methyl Ester.—A similar experiment was carried out with the above compounds (**3c** and **2a**) using free valine methyl ester as nucleophile (solution 0.204 *M* in **3c** or **2a** and 2.04 *M* in valine methyl ester); **3c** reacted within the time of mixing of the reagents ($t_{1/2}$ less than 10–15 sec), while **2a** condensed more slowly ($t_{1/2}$ 268 sec) (0.2-mm KBr cells).

C. Condensation with Benzylamine.—When **3c** and **2a** were reacted in the above conditions using benzylamine as nucleophile (solutions 0.109 *M* in **3c** or **2a** and benzylamine), **3c** gave $t_{1/2}$ of 10–15 sec, whereas **2a** gave $t_{1/2}$ of 454 sec (0.1-mm KBr cells).

Registry No.—**2a**, 28897-80-5; **2b**, 28897-81-6; **3a**, 28897-82-7; **3b**, 28897-83-8; **3c**, 28897-87-2; **3d**, 28897-88-3; AcA-L-Ala-OH, 3103-37-5; AcA-L-Val-OH, 3103-33-1; AcA-L-Leu-OH, 1803-64-1; AcA-L-Phe-OH, 17667-55-9; *N*-acetoacetyl-L-leucylglycine ethyl ester, 1803-65-2; *N*-acetoacetyl-L-valyl-L-valine methyl ester, 21761-28-4; *N*-acetoacetyl-L-leucine benzylamide, 28897-86-1.

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Synthesis of 1,2- and 2,4-Disubstituted Adamantanes. The Protoadamantane Route[1,2]

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A number of 1,2-disubstituted adamantanes have been prepared easily by using the facile rearrangement of 4-substituted protoadamantanes as the synthetic principle. The conversion of 4-methylprotoadamantan-4-ol (**3**) to the 1-methyladamantane 2-substituted alcohol **4**, bromide **5**, acetamide **6**, amine **7**, and ketone **8** are high-yield processes. The reaction of 4-protoadamantanone (**2**) with PCl_3–PCl_5 afforded 4-chloroprotoadamantene (**10**) as well as the 1,2-dichloroadamantane (**11**) rearrangement product. The dichloride (**11**) was also prepared by reaction of thionyl chloride on adamantane-1,2-diol (**13**). In addition, the Ritter reaction on adamanto[2,1-*d*]oxazolidin-2-one (**1**) gave 1-*N*-acetyladamantane-1,2-diamine hydrochloride (**14**) and its hydrolysis product, adamantane-1,2-diamine dihydrochloride (**15**). 2,4-Disubstituted adamantanes can also be prepared *via* protoadamantane precursors. Starting from protoadamantene (**19**), epoxidation followed by acid hydrolysis afforded adamantane-2a,4a-diol (**27**). Bromination of protoadamantene (**19**) gave a 2:1 ratio of 2a,4a-dibromoadamantane (**23**) and 2e,4a-dibromoadamantane (**25**).

In recent years the synthesis of a number of 1,2-disubstituted adamantane derivatives[1,2,4-10] has been reported. These compounds are difficult to obtain by the usual substitution procedures utilized in adamantane chemistry.[11] For example, ionic substitution of 1-adamantane derivatives tends to give bridgehead substitution exclusively to yield 1,3 products.[11] Free-radical substitution of 1-adamantane derivatives gives a difficult-to-separate mixture of products rich in 1,3 and 1,4 derivatives,[12] whereas radical bromination of adamantanone gives a mixture of all the possible monobrominated adamantanones.[13]

The most successful general approach is based on the work of Curran and Angier[4] who prepared adamanto-[2,1-*d*]oxazolidin-2-one (**1**) by an intramolecular nitrene insertion process.[14] The availability of **1** afforded an opportunity to prepare many other 1,2-difunctional derivatives.[4,7,8] While we record here the preparation of two new 1,2-difunctional derivatives *via* this versatile starting material, we wish to describe a new synthetic route based on rearrangement from protoadamantane precursors.

A second class, 2,4-disubstituted adamantanes, has been synthesized either by addition reactions to 2,4-dehydroadamantane[15] or by the π-route closures of bicyclo[3.3.1]non-3-en-7-acylium ions, generated from 4-oxohomoadamantan-5-one in sulfuric acid.[16] A new synthetic route to such compounds based on protoadamantane precursors has also been developed.

Results and Discussion

4-Protoadamantanone (**2**) is now readily available.[1a,17-19] Rearrangement of protoadamantanes to adamantanes generally occurs readily because of the greater thermodynamic stability of the adamantane skeleton.[1a,17]

This principle can be put to synthetic advantage. For example, 4-methylprotoadamantan-4-ol (**3**), an isomeric mixture obtained by the Grignard reaction on **2**, is readily converted by the action of aqueous acid to 1-methyladamantan-2-ol (**4**) (see Scheme I). If ethereal HBr is employed, the product is the corresponding bromide **5**. The Ritter reaction on **3** gives amide **6** which can be converted to amine **7**. 1-Methyladamantan-2-one (**8**) can be prepared easily in one step by chromic acid oxidation of **3**, or the rearrangement product **4** can be isolated and then oxidized.

All of these reactions proceed cleanly and with high yield and therefore offer a new pathway to the synthesis of 1-alkyl-2-adamantyl compounds. The only method reported for the preparation of 1-methyl-2-adamantanes utilizes a sulfuric acid oxidation of 1-methyladamantane.[20] 1-Methyladamantan-2-one (**8**) is obtained in very low yield (3-5%) and is very difficult to separate from the other oxidation products.[21] The nmr spectra of the rearranged products **4**–**8** are consistent with their proposed structures. Whereas the spectra of the epimeric alcohols **3** are complex and show the methyl singlets at τ 8.75 and 8.61 for the 4-exo and 4-endo epimers,

(1) Paper III of a series on protoadamantane chemistry. (a) Paper I, D. Lenoir and P. v. R. Schleyer, *Chem. Commun.*, 941 (1970). (b) Paper II reported this work in preliminary communication form, D. Lenoir, P. v. R. Schleyer, C. A. Cupas, and W. E. Heyd, *ibid.*, 26 (1971).

(2) Dr. M. A. McKervey has kindly informed us of work similar to that reported here: B. D. Cuddy, D. Grant, and M. A. McKervey, *ibid.*, 27 (1971).

(3) (a) NIH International Postdoctoral Fellow, 1969–1970; (b) NIH Postdoctoral Fellow, 1969–1970; (c) CNRS and NATO Postdoctoral Fellow, 1970–1971.

(4) W. V. Curran and R. B. Angier, *Chem. Commun.*, 563 (1967); W. V. Curran and R. B. Angier, *J. Org. Chem.*, **34**, 3668 (1969).

(5) M. A. McKervey, *Chem. Ind. (London)*, 1791 (1967).

(6) W. H. W. Lunn, W. D. Podmore, and S. S. Szinai, *J. Chem. Soc. C*, 1657 (1968).

(7) P. v. R. Schleyer and V. Buss, *J. Amer. Chem. Soc.*, **91**, 5880 (1969); V. Buss, R. Gleiter, and P. v. R. Schleyer, *ibid.*, in press.

(8) J. C. Martin and B. R. Ree, *ibid.*, **91**, 5882 (1969); B. R. Ree and J. C. Martin, *ibid.*, **92**, 1660 (1970).

(9) H. Stetter, H. G. Thomas, and K. Meyer, *Chem. Ber.*, **103**, 863 (1970).

(10) J. K. Chakrabarti, S. S. Szinai, and A. Todd, *J. Chem. Soc. C*, 1303 (1970).

(11) See reviews: (a) R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964); (b) R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forsch.*, in press.

(12) I. Tabushi, T. Okada, Y. Aoyama, and R. Oda, *Tetrahedron Lett.*, 4069 (1969).

(13) (a) I. Tabushi, personal communication; (b) D. Lenoir, unpublished results.

(14) (a) Other intramolecular processes have already been reported that give four- and five-membered rings fused to the adamantane skeleton.[6,10,14b] (b) R. B. Gagonan, J. C. Dalton, and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 4752 (1970).

(15) A. C. Udding, J. Starting, and H. Wynberg, *Tetrahedron Lett.*, 1345 (1968).

(16) M. A. McKervey, D. Faulkner, and H. Hamill, *ibid.*, 1971 (1970).

(17) M. L. Sinnot, H. J. Storesund, and M. C. Whiting, *Chem. Commun.*, 1003 (1969).

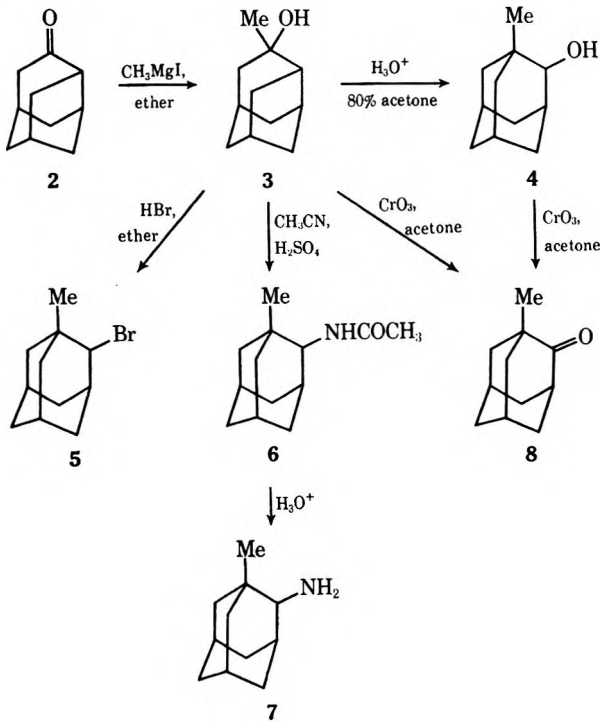
(18) R. M. Black and G. B. Gill, *ibid.*, 972 (1970).

(19) W. H. W. Lunn, *J. Chem. Soc. C*, 2124 (1970).

(20) H. W. Geluk and J. L. M. A. Schlatmann, *Recl. Trav. Chim. Pays-Bas*, **88**, 13 (1969).

(21) (a) E. Osawa, unpublished results; (b) D. Lenoir and S. Pouls, unpublished results.

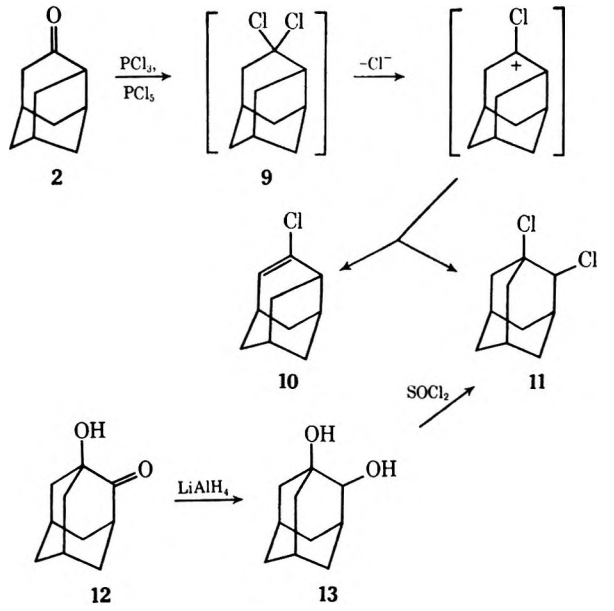
SCHEME I



respectively, the spectra of **4**–**8** are considerably simpler and the methyl protons are more shielded.

No synthesis of a 1,2-dihaloadamantane has been reported in the literature; the "protoadamantane route" provides a method of preparation. Reaction of 4-protoadamantanone (**2**) with a PCl_3–PCl_5 mixture at 0° gives a 2:1 mixture of the chlorinated products **10** and **11** which can be separated either by column-chromatography on silica gel or by preparative glpc (see Scheme II). This result is somewhat surprising,

SCHEME II

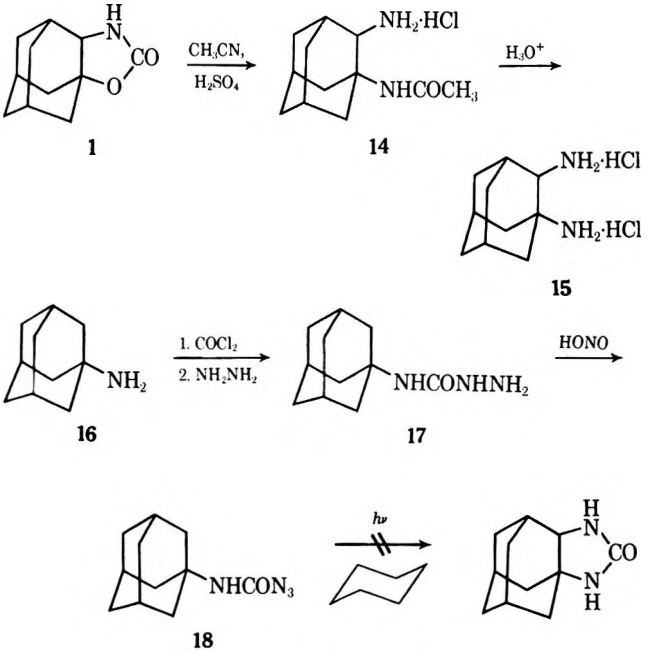


since all the other 4-protoadamantyl derivatives studied rearranged almost completely to the 2-adamantyl isomers. A possible intermediate, 4,4-dichloroprotoadamantane (**9**), could not be isolated under the conditions utilized.

Besides undergoing the usual rearrangement to product **11**, the cation arising from **9** can eliminate a proton from C-5 to give olefin **10**. The nmr spectrum of compound **10** is consistant with its proposed structure and shows a four-line pattern (A part of an AMN spectrum) of one vinylic proton centered at τ 3.79 ($J_{H\text{-}5,H\text{-}6}$ = 8 Hz and $J_{H\text{-}5,H\text{-}3}$ = 1.8 Hz). The structure of 1,2-dichloroadamantane (**11**) was proven by synthesizing this compound by an unambiguous route. 2-Ketoadamantan-1-ol (**12**)[7,8] was reduced with $LiAlH_4$ in ether to adamantane-1,2-diol (**13**). This was converted to **11** (*ca.* 45% yield) by treatment with $SOCl_2$.

The preparation of diamine **15** involved the reaction of **1** under Ritter conditions (Scheme III). This afforded 1-*N*-acetyladamantane-1,2-diamine isolated as the hydrochloride salt **14**. Acid hydrolysis of **14** yielded adamantane-1,2-diamine as the dihydrochloride monohydrate salt **15**. Attempts to prepare this diamine in a more direct way by the photolysis of **18** under the conditions tried (Scheme III) were not successful. Despite the obvious similarity between this route and that used to prepare **1** (as well as that used to prepare a fused five-membered ketone[10]), photolysis of **18** under similar conditions led to a mixture of products which nmr indicated chiefly to result from nitrene insertion into the cyclohexane used as solvent. Change of solvent to benzene still gave a complex mixture of photolysis products. Even the insertion reaction reported by Curran and Angier[4] gives an intermolecular nitrene insertion into the solvent (*ca.* 40%) besides the formation of **1**. The photochemical decomposition of carbamoyl azide (NH_2CON_3) in alcoholic solvents was reported to give a mixture of products arising from nitrene insertion into the solvent and from HN_3 elimination.[22] The conformation of the intermediate nitrene from **18** may be trans, precluding intramolecular attack.

SCHEME III

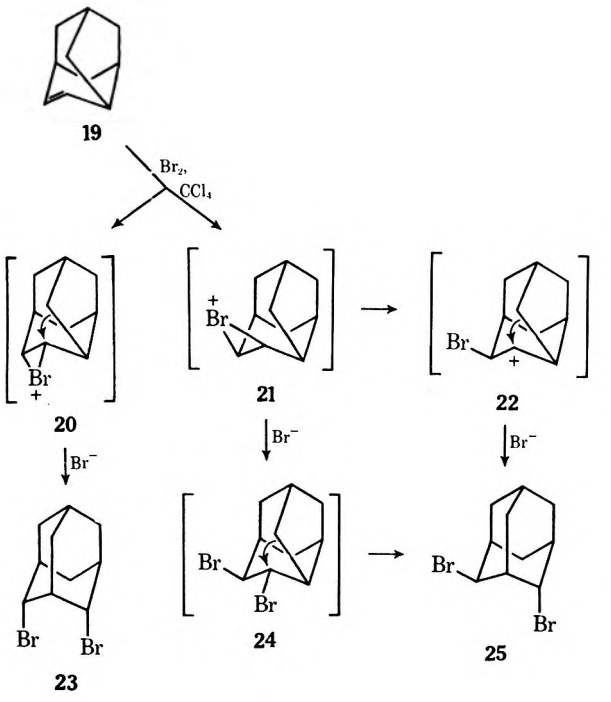


Protoadamantene (**19**)[1] is available by the Wolff–Kishner reduction of the ketone mixture arising from the thermal rearrangement of allyloxycyclohepta-

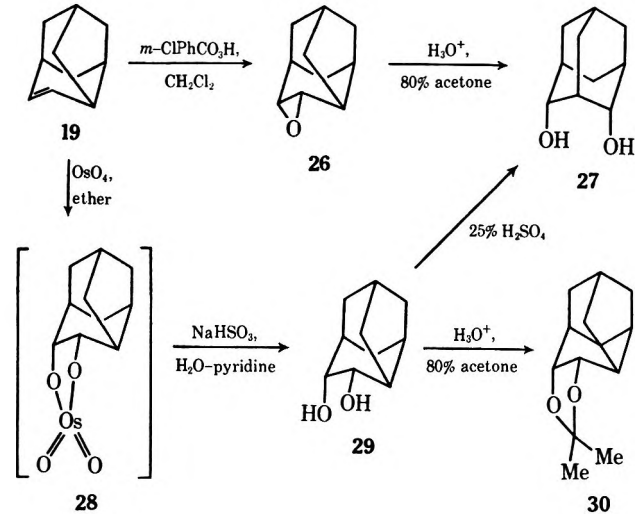
(22) R. Kreher and G. H. Berger, *Tetrahedron Lett.*, 369 (1965).

triene.[23] Recently, the synthesis of **19** in 34% yield by the pyrolysis of 4-protoadamantyl xanthate has also been reported.[15,24] Protoadamantene (**19**) proves to be a valuable starting material for the synthesis of 2,4-disubstituted adamantanes (Schemes IV and V).

SCHEME IV



SCHEME V



Treatment of **19** with 1 mol of bromine in CCl_4 gave a 2:1 mixture of the isomeric dibromides, 2a,4a-dibromoadamantane (**23**) and 2a,4e-dibromoadamantane (**25**).[1b,2] Whereas the formation of 2a,4e-dibromoadamantane (**23**) can be explained best by the ring opening of the *exo*-4,5-protoadamantyl bromonium ion **20** shown, the 2a,4e isomer **25** can be visualized as being formed by two plausible mechanistic pathways. In the first pathway, the *endo*-4,5-protoadamantane bromonium ion **21**, formed from **19** along with **20**, undergoes nucleophilic attack to give *trans*-4,5-dibromoprotoadamantane (**24**). This dibromide would be expected to be quite unstable toward rearrangement with internal return to **25**. The endo bromonium ion **21** could open to the *endo*-5-bromoprotoadamant-4-yl cation **22**; "leakage" allowing bond migration and nucleophilic bromide attack would give **25**. There is evidence for such a "leakage" mechanism in the solvolysis of *endo*-4-protoadamantyl derivatives.[1a]

m-Chloroperbenzoic acid reacts with **19** in methylene chloride to give a protoadamantane 4,5-epoxide product; the exo isomer **26** is the major constituent of this mixture, along with a minor amount of the endo isomer. The configuration of the major isomer was demonstrated by $LiAlH_4$ reduction of the epoxide mixture; the main product was *exo*-protoadamantan-4-ol. Treatment of epoxide **26** with 80% aqueous acetone containing a trace of HCl afforded adamantane-2a,4a-diol (**27**), rather cleanly. It is reasonable that diol **27** is formed by ring opening of the *exo*-4,5-protoadamantyl oxonium ion (**26** H^+) with concurrent skeletal rearrangement and nucleophilic attack by water.

Protoadamantene (**19**) reacts with OsO_4 in ether almost instantaneously to form a black osmate **28** precipitate (see Scheme V). The osmate **28** was cleaved with $NaHSO_3$ in 50% aqueous pyridine to give *exo*-protoadamantane-4,5-*cis*-diol (**29**). The configuration of the diol **29** was determined by analysis of the nmr spectral pattern of the protons at C-4 and C-5.[25] Attempted rearrangement of **29** to the more stable adamantane-2a,4a-diol (**27**) by refluxing with 80% aqueous acetone containing a trace of hydrochloric acid gave acetonide **30** instead of **27**. The rearrangement of **29** to **27** had to be carried out under more vigorous conditions: 25% sulfuric acid and a temperature of 100°. However, after 1.5 hr **29** gave a 80% crude yield of **27**.

Special aspects of the spectral features of **23** and of **27** have already been commented on in the preliminary communication.[1b]

The examples we have presented in this paper demonstrate that both 1,2- and 2,4-disubstituted adamantanes can be prepared readily from protoadamantane precursors.

Experimental Section

Routine infrared spectra were taken on a Perkin-Elmer 237B spectrophotometer and were run in KBr pellets unless specified. Higher resolution infrared spectra were taken of some compounds on a Perkin-Elmer 421 double-beam spectrophotometer. Unless otherwise stated, pmr spectra were taken in $CDCl_3$ with TMS acting as internal standard and were recorded on a Varian A-60A spectrometer. Mass spectra were taken on an AEI MS-9 spectrometer at 150° and 70 eV. With $(C_4F_9)_3N$ as reference, high-resolution mass spectral analyses were performed on the parent peaks of some compounds, and the calculated values were taken from J. H. Beynon and A. E. Williams, "Mass and Abundance Tables for Use in Mass Spectrometry," Elsevier, Amsterdam, 1963. Melting points were determined on a Mettler FP1 apparatus in a sealed capillary and are uncorrected. Elemental analyses were determined by G. Robertson, Florham Park, N. J.

4-Methylprotoadamantan-4-ol (3).—Methylmagnesium iodide was prepared by reaction of 0.486 g of magnesium and 2.84 g of methyl iodide in 20 ml of absolute ether. To this solution 1.0 g (6.7 mmol) of 4-protoadamantanone (**2**),[1a,17-19] dissolved in 20 ml of ether, was added dropwise during 10 min with stirring.

(23) C. A. Cupas, W. Schuman, and W. E. Heyd, *J. Amer. Chem. Soc.*, **92**, 3237 (1970).

(24) Pyrolysis of 2-adamantyl trifluoroacetate at 350° gives a hydrocarbon fraction (*ca.* 30%) which consists of nearly equal amounts of adamantane, 2,4-dehydroadamantane, and protoadamantene: D. Raber, unpublished results.

(25) D. Lenoir and P. v. R. Schleyer, unpublished results.

The mixture was refluxed for 2 hr and worked up by addition of 10 ml of saturated ammonium chloride solution. The ether phase was separated, washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give 1.02 g (94%) of crude 4-methylprotoadamantan-4-ol (**3**). After sublimation *in vacuo*, glpc revealed that the solid consisted of two products in the ratio of 2:1. These were shown to be the epimeric 4-exo and 4-endo alcohols, respectively.[13a] Complete experimental details on the separation and characterization of the epimeric alcohols **3** will be published elsewhere.[25] The mixture of the epimeric alcohols **3** was used without further separation. The nmr of the 4-endo alcohol showed a complex multiplet with broad peaks at τ 7.80, 7.90, 8.12, 8.20, 8.40, 8.50 (m, 15, protoadamantyl H and OH), and 8.61 (s, 3, CH_3). The nmr of the 4-exo alcohol showed a complex multiplet with broad peaks at τ 7.80, 7.93, 8.10, 8.25, 8.50, 8.68 (m, 15, protoadamantyl H and OH), and 8.75 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.10; H, 10.60. Found: C, 79.46; H, 10.91.

1-Methyladamantan-2-ol (4).—To 0.50 g (3.0 mmol) of **3** dissolved in 20 ml of 80% aqueous acetone, 1 drop of concentrated hydrochloric acid was added and the mixture refluxed for 10 min. The solution was concentrated *in vacuo* to a small volume, and then the mixture was extracted with ether. After drying over anhydrous sodium sulfate and evaporation *in vacuo*, 0.48 g of crude product was obtained. Sublimation *in vacuo* gave 0.43 g (85%) of 1-methyladamantan-2-ol (**4**): mp 168.5–170.0°; nmr τ 6.52 (broad s, 1, CHOH), complex multiplet with broad peaks at 8.50, 8.40, 8.20 (m, 15, adamantyl H and OH), and 9.12 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 166 (27, M^+) (measured 166.1358, calcd for $C_{11}H_{18}O$ 166.1356, 151 (15), 148 (100), 133 (22), 119 (5), 107 (14), 106 (22), 105 (16), 93 (58), and 79 (24).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.10; H, 10.60. Found: C, 79.12; H, 10.50.

1-Methyladamant-2-yl Bromide (5).—To 0.20 g (1.2 mmol) of **3**, 10 ml of ether saturated with hydrogen bromide was added. The solution was refluxed for 30 min, and evaporated *in vacuo*, and the residue sublimed to give 0.21 g (76%) of 1-methyladamant-2-yl bromide (**5**): mp 99–101°; nmr τ 5.60 (broad s, 1, CHBr), 7.76 (broad s, 1, CHCHBr), complex multiplet with broad peaks at 8.25, 8.10 (m, 14, adamantyl H), and 9.10 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48; Br, 34.87. Found: C, 57.58; H, 7.38; Br, 34.74.

***N*-Acetyl-1-methyladamantane-2-amine (6).**—To 4 ml of acetonitrile, cooled in an ice bath, 1.5 ml of concentrated sulfuric acid was added dropwise with stirring, followed by 0.161 g (0.96 mmol) of **3**. The reaction mixture was allowed to warm and was kept at room temperature for 3 hr. After quenching in ice, a 10% solution of potassium hydroxide was added until basic pH, causing a solid to precipitate. The mother liquor was filtered off and the solid residue washed two times with water. The wet solid was dissolved in 5 ml of absolute ethanol and evaporated *in vacuo* to remove any water present. Sublimation *in vacuo* of the residue gave 0.170 g (90%) of *N*-acetyl-1-methyladamantane-2-amine (**6**): mp 139–141°; ir 3320 (NH), 1640 (C=O), and 1550 cm^{-1} (NH, b); nmr τ 4.0 (broad s, 1, NHCOMe), 6.12 (broad d, 1, J = 10 Hz, CHNHCOMe), 7.99 (s, 3, $NHCOCH_3$), 7.9–9.0 (m, 13, adamantyl H), and 9.33 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 207 (100, M^+), 192 (6), 164 (8), 148 (43), 133 (22), 119 (5) 107 (14), 106 (22), 105 (16), 93 (58), and 79 (24).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.79. Found: C, 75.37; H, 10.49; N, 6.99.

1-Methyladamantane-2-amine (7).—To 84 mg (0.4 mmol) of **6**, 9 ml of concentrated hydrochloric acid and 2 ml of methanol were added. The mixture was heated to reflux with stirring for 3 days and then cooled. After addition of excess potassium hydroxide, the aqueous solution was extracted three times with chloroform (50 ml each). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and evaporated to yield a solid. Sublimation of the residue gave 60 mg (90%) of 1-methyladamantyl-2-amine (**7**): mp 140–142°; ir (Nujol mull) 3400 (broad NH) and 1605 cm^{-1} (NH, b asym); nmr τ 7.37 (broad s, 1, $CHNH_2$), 7.9–9.0 (m, 15, adamantyl H and NH_2), and 9.21 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 165 (100, M^+), 164 (89), 148 (89), 133 (24), 119 (8), 106 (30), 105 (24), 93 (40), 92 (34), and 79 (20). The amine **7** was submitted for elemental analysis as the hydrochloride salt which was prepared in the same manner as in **15**.

Anal. Calcd for $C_{11}H_{20}NCl$: C, 65.49; H, 9.99; N, 6.94. Found: C, 65.61; H, 9.95; N, 7.06.

1-Methyladamantan-2-one (8).—To 1.0 g (6.0 mmol) of **3** dissolved in 10 ml of acetone, 3 ml of Jones-type reagent[26] was added, and the mixture was stirred for 2 hr at room temperature. To reduce the excess chromic oxide, 5 ml of methanol was added upon work-up. The solution was diluted with 50 ml of water and extracted five times with chloroform (15 ml each). The combined organic layers were washed with potassium bicarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The crude product was purified by chromatography on a 50-g silica gel column, with *n*-pentane and *n*-pentane–2% ether as eluents. Evaporation of the main fraction yielded 0.84 g of purified ketone. Sublimation of the residue gave 0.81 g (80%) of 1-methyladamantan-2-one (**8**) as a waxy, colorless solid: mp 106.5–108.5°; ir (CCl_4) 1729 cm^{-1} (C=O); nmr τ 7.76 (broad s, 1, CHC=O), a complex multiplet with broad peaks at 7.87, 8.07 (m, 12, adamantyl H), and 9.00 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 164 (100, M^+), 149 (9), 136 (8), 135 (7), 131 (8), and 93 (91).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.38; H, 9.80.

Compound **8** was also prepared by oxidation of the rearranged alcohol **4**. To 0.10 g (0.6 mmol) of **4** dissolved in 5 ml of acetone, 0.5 ml of Jones-type reagent[26] was added, and the mixture stirred for 1 hr at room temperature. Using the work-up described for the direct rearrangement oxidation of **3**, 0.08 g (80%) of **8** was obtained, mp 104–106°. The ketone formed by this route was shown by glpc coinjection, ir, and mixture melting point to be identical with that obtained by the direct rearrangement–oxidation of **3**.

Chlorination of 4-Protoadamantanone (2).—To 1.00 g (6.7 mmol) of **2**, 4 ml of phosphorus trichloride was added with stirring at 0°. Following the addition of 3.6 g of phosphorus pentachloride added during 5 min, the reaction mixture was stirred for 10 hr at 0° and then was allowed to warm. Stirring was continued at room temperature for 2 hr, after which the mixture was cooled to 0° and the excess Lewis acid was hydrolyzed by addition of ice. After extraction five times with ether (25 ml each), the combined organic layers were washed with 15 ml of saturated potassium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and then filtered. Evaporation of the solvent gave 0.8 g of crude solid which was shown by analytical glpc (column, 10% Carbowax 20M on Chromosorb W 30–60) to consist mainly (>95%) of two products in the ratio of 2:1. Separation of the mixture on a column of 30 g of silica gel gave two main fractions when eluted with pentane. Upon evaporation of the eluent, the less polar product consisted of 0.41 g of the crude liquid 10 and the more polar product consisted of 0.24 g of the crude solid 11.

4-Chloroprotoadamantene (10).—The less polar crude fraction of the reaction product from phosphorus trichloride–phosphorus pentachloride and 4-protoadamantanone (**2**) was purified by preparative glpc (column, 15% FFAP, Chromosorb W 60–80) to give an analytical sample of 4-chloroprotoadamantene (**10**): $n^{25}D$ 1.5331; ir (thin film) 3050 (=CH), 1640 (C=C), and 830 cm^{-1}(CH, out of plane torsion); nmr shows a four-line pattern centered at τ 3.79 (m, 1, C=CH, $J_{H\text{-}5,H\text{-}6}$ = 8 Hz and $J_{H\text{-}5,H\text{-}3}$ = 1.8 Hz) and 7.0–8.5 (m, 12, adamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 170 (13, M^+), 168 (44, M^+), 153 (3), 139 (3), 133 (88), 126 (37), 113 (28), 105 (10), and 91 (100).

Anal. Calcd for $C_{10}H_{13}Cl$: C, 71.21; H, 7.77; Cl, 21.02. Found: C, 71.31; H, 8.04; Cl, 20.99.

1,2-Dichloroadamantane (11).—The more polar crude fraction of the reaction product from phosphorus trichloride–phosphorus pentachloride and 4-protoadamantanone (**2**) was purified two times by chromatography on a 20-g silica gel column (eluted with pentane) to give an analytical sample of 0.10 g (7%) of 1,2-dichloroadamantane (**11**): mp 183–185° dec; ir 850, 780, 740, and 690 cm^{-1} (strong CCl); nmr τ 5.50 (broad s, 1, CHCl) and 7.0–8.7 (broad m, 13, adamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 208 (1, M^+), 206 (5, M^+), 204 (9, M^+), 171 (30), 169 (100), 133 (15), 127 (4), 115 (3), 113 (7), 105 (4), 91 (16), 79 (11), and 77 (8).

(26) C. Djerassi, P. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

Anal. Calcd for $C_{10}H_{14}Cl_2$: C, 58.55; H, 6.88; Cl, 34.57. Found: C, 58.29; H, 6.90; Cl, 34.51.

Adamantane-1,2-diol (13).—To a suspension of 0.08 g of lithium aluminum hydride in 5 ml of anhydrous ethyl ether, 0.12 g (0.72 mmol) of 2-ketoadamantan-1-ol (12)[5,6] dissolved in 7 ml of anhydrous ethyl ether was added and the mixture refluxed overnight. After the usual work-up,[27] sublimation *in vacuo* gave 0.11 g of diol 13. An analytical sample was obtained by chromatography on a 20-g silica gel column which was eluted with ethyl ether. Evaporation of the solvent gave 0.10 g (83%) of adamantan-1,2-diol (13): mp 328–330°; ir (dilute CCl_4) 3644, 3627, 3607, 3585, and 3564 cm^{-1} (O-H);[28] nmr (DMSO-d_6) τ 5.71 (d, 1, 2 OH, J = 3 Hz), 5.95 (s, 1, 1 OH), 6.56 (broad s, 1, CHOH), and 7.8–9.0 (m, 15, adamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 168 (100, M^+), 152 (14), 150 (35), 137 (3), 111 (5), 110 (6), 108 (8), 107 (5), 95 (84), 94 (14), and 79 (7).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.63; H, 9.74.

Chlorination of Adamantane-1,2-diol.—To 37 mg of 13, 2 ml of thionyl chloride was added and the reaction mixture was heated to reflux overnight. The excess thionyl chloride was distilled off and the crude product was analyzed by glpc (column, 10% Carbowax 20M on Chromosorb W 30–60). Two peaks in the ratio of 3:2 were observed, and the more polar product showed the same retention time as the 1,2-dichloride 11 (by coinjection). The crude reaction mixture was purified by chromatography on a 20-g silica gel column and pentane was used as the eluent. Evaporation of the solvent of the more polar fraction gave an analytical sample of 1,2-dichloroadamantane (11). The 1,2-dichloride formed by this route was shown by glpc coinjection, ir, and melting point to be identical with that obtained *via* the reaction of phosphorus trichloride–phosphorus pentachloride and 2.

1-*N*-Acetyladamantane-1,2-diamine Hydrochloride (14).—To 8 ml of acetonitrile, cooled in an ice bath, 3 ml of concentrated sulfuric acid was added dropwise with stirring, followed by 0.50 g (2.6 mmol) of adamanto[2,1-*d*]oxazolidin-2-one (1).[2] The reaction mixture was allowed to warm and was kept at room temperature for 3 hr. After quenching in ice–water, potassium hydroxide solution was added until the solution was pH 9 and then the aqueous mixture was extracted three times with chloroform (75 ml each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield an oil. The oil was dissolved in 10 ml of acetone and filtered, and then concentrated hydrochloric acid was added dropwise until the solution was acidic. Upon addition of *ca.* 40 ml of ether, a small amount of amorphous solid separated. After filtration, the filtrate was cooled in a refrigerator, and a crystalline solid separated which was recrystallized from ethanol/acetone–ether to give 0.15 g (23%) of 1-*N*-acetyladamantane-1,2-diamine hydrochloride (14): mp >300° dec; ir 3470 (broad, NH), 3250 (NH amide), 3020 (weak, NH amide), 2010 (NH_3^+, b and torsion), 1655 (C=O), 1600 (NH amine, b asym), 1540 (NH amide, b), and 1495 cm^{-1} (NH amine, b sym); nmr (D_2O, DSS internal standard) τ 5.65 (s, 1, $CHNH_3^+$), 7.25–8.50 (m, 11, adamantyl H and amide H), and 7.95 (s, 3, $NHCOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 208 (34, M^+ of free amine) (measured 208.15775, calcd for $C_{12}H_{20}N_2O$ 208.157555), 191 (8), 165 (7), 149 (100), 136 (17), 120 (4), 107 (13), and 94 (10).

Anal. Calcd for $C_{12}H_{21}N_2OCl$: C, 58.88; H, 8.65; N, 11.44. Found: C, 58.81 H, 8.65; N, 11.18.

Adamantane-1,2-diamine Dichloride Monohydrate (15).—To 10 ml of 6 *N* hydrochloric acid, 125 mg (0.5 mmol) of 14 was added. The reaction mixture was heated to reflux for 33 hr and then cooled. After addition of excess potassium hydroxide solution, the aqueous mixture was extracted three times with chloroform (50 ml each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a solid. The solid was dissolved in 10 ml of acetone and then filtered. Upon addition of concentrated hydrochloric acid (added dropwise until the solution was acidic), a solid separated which was recrystallized from ethanol/acetone–ether to give 75 mg (61%) of adamantane-1,2-diamine dihydrochloride monohydrate (15): mp >300° dec; ir 3425 (broad, NH), 1965 (NH_3^+, b and torsion), 1575 (NH, b asym), and 1500 cm^{-1} (NH, b sym); nmr (D_2O, DSS as internal standard) τ 6.22 (m, 1, $CHNH_3^+$, $\nu_{1/2}$ = 6 Hz) and 7.50–8.30 (m, 13, adamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 166 (100, M^+ of free diamine) (measured 166.146777, calcd for $C_{10}H_{18}N_2$ 166.146991), 149 (20), 136 (6), 123 (4), 120 (4), 110 (10), 109 (43), 108 (8), 107 (10), 106 (12), and 95 (8).

Anal. Calcd for $C_{10}H_{20}N_2Cl_2 \cdot H_2O$: C, 46.69; H, 8.62; N, 10.89. Found: C, 46.36; H, 8.81; N, 10.52.

4-(Adamant-1-yl) Semicarbazide (17).—To 18.8 g (0.1 mol) of adamantane-1-amine hydrochloride (16) dissolved in 100 ml of water, excess potassium hydroxide solution was added, and the solid which separated was extracted five times with chloroform (100 ml each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a solid. The solid was dissolved in 400 ml of benzene, dried over anhydrous magnesium sulfate, filtered, and transfered to 1-l. three-neck flask having a drying tube. The reaction vessel was cooled in an ice bath, 7.9 g (0.1 mol) of pyridine was added, and then 100 ml of 12% phosgene solution in benzene was dripped in under stirring. After 30 min, the solid pyridinium hydrochloride which had precipitated was filtered off, and the filtrate was evaporated *in vacuo* to remove excess phosgene. The solid residue was dissolved in 100 ml of benzene and was dripped into a solution of 30 ml of absolute hydrazine in 100 ml of benzene at room temperature with stirring. After stirring for 4 hr, the mixture was filtered and the filtrate was evaporated *in vacuo* to yield a solid which was recrystallized from ethanol to give 4.8 g (23%) of 4-(adamant-1-yl) semicarbazide (17): mp 167–168.5°; ir 3280 (NH), 1650 (NH, b asym), 1620 (C=O), and 1540 cm^{-1} (NH, b sym); mass spectrum (70 eV) *m/e* 209 (M^+).

Anal. Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 62.85; H, 8.99; N, 20.39.

1-Adamantylcarbamoyl Azide (18).—To 3.06 g (14.6 mmol) of 17 dissolved in 50 ml of glacial acetic acid, 140 ml of water was added, followed by 9 ml of concentrated hydrochloric acid. While the solution was stirred in an ice bath, a solution of 1.06 g of sodium nitrite in 15 ml of water was added and then a solid separated. After the reaction mixture stirred for 1 hr, the solution was extracted five times with chloroform (50 ml each). The combined organic layers were washed with a 5% sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* at 30° to give 2.6 g (80%) of carbamoyl azide 18, mp 144–147°. A small amount was recrystallized from cyclohexane to give an analytical sample of 1-adamantylcarbamoyl azide (18): mp 145–147°; ir 3350 (NH), 3020 (weak, NH), 2150 (N=N=N, asym), 1710 (C=O), 1520 (NH, b), and 1220 cm^{-1} (N=N=N, sym).

Anal. Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 60.16; H, 7.65; N, 25.63.

Photolysis of 1-Adamantylcarbamoyl Azide (18).—To 2.5 g (1.1 mmol) of 18, 800 ml of cyclohexane was added, and the solution was poured into a quartz photolysis reaction vessel having a drying tube. The solution was photolyzed using a water-jacketed mercury lamp for 24 hr. At the termination of the photolysis period, a solid was observed in the vessel. Evaporation of the solvent *in vacuo* gave an amorphous solid. Analytical glpc (10% Carbowax 20M on Chromosorb W 30–60) showed a complex mixture of at least nine products. Repeated efforts to separate this mixture by crystallization were unfruitful. The nmr spectra of the vacuum-oven dried solid mixture indicated τ 7.6–8.1 (complex m), 8.12 (broad s), and 8.56 (sharp s, cyclohexyl H). A similar uncrystallized complex reaction mixture was obtained when 3.0 g of 18 were photolyzed in 400 ml of benzene and 30 ml of ether for 20 hr. Upon hydrolysis of the amorphous photolysis residue in 3 *N* hydrochloric acid for 3 hr, no diamine 15 could be isolated.

Bromination of Protoadamantene (19).—To 134 mg (1 mmol) of protoadamantene (19)[22] dissolved in 100 ml of carbon tetrachloride, 0.05 ml of bromine was added at room temperature with stirring. Bromine was immediately decolorized during dropwise addition. Analytical glpc of the reaction mixture showed two peaks in a 1:2 ratio. After evaporation of the solvent, the product mixture was separated by chromatography on a column of 20 g of silica gel. Elution with *n*-pentane gave 91 mg of a less polar crude solid, the axial-equatorial dibromide 25. Further

(27) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 584.

(28) The characterization of the free and hydrogen-bonded O–H bands will be published elsewhere: T. Gorrie and P. v. R. Schleyer, to be published.

elution with a solution of 90% *n*-pentane and 10% ether (v/v) gave 156 mg of a more polar crude solid, the diaxial isomer **23**.

2a,4a-Dibromoadamantane (23).—The more polar chromatography fraction described above was purified by crystallization from *n*-pentane to give 123 mg (42%) of 2a,4a-dibromoadamantane (**23**) as colorless needles: mp 171.8–173.0° (reported 171–172°[2]); nmr τ 5.35 (broad s, 2, CHBr, calcd 5.45[29]), 7.16 (broad downfield AB d, 1, H-9a,[30] J = 16 Hz, calcd 7.09[29]), 7.32 (broad s superimposed on right part of downfield AB d, 1, H-3, calcd 7.59[29]), 7.67 (broad s, 2, H-1 and H-5, calcd 7.86[29]), 8.05 ± 0.23 with large peak at 8.00 (m, 7, H-10a,e, calcd 7.93,[29] and H-6a,e, H-8a,e, calcd 8.07,[29] and H-7, calcd 8.15[29]), and 8.26 (upfield AB d, the left part superimposed on m, 1, H-9e, calcd 8.51[29]); mass spectrum (70 eV) *m/e* (rel intensity) 296 (8, M^+), 294 (16, M^+), 292 (9, M^+), 215 (98), 213 (100), 133 (51), 105 (16), 91 (69), and 79 (32).

Anal. Calcd for $C_{10}H_{14}Br_2$: C, 40.85; H, 4.80; Br, 54.35. Found: C, 41.00; H, 4.95; Br, 54.55.

2a,4e-Dibromoadamantane (25).—The less polar crude fraction of the reaction product from the bromination of **19** was sublimed *in vacuo* to give 85 mg (29%) of 2a,4e-dibromoadamantane (**25**): mp 119–121° (lit.[15] 120–122°); nmr τ 4.80 (s, 1, H-4a,[30] lit.[29] 4.85), 5.21 (s, 1, H-2, lit.[29] 5.27), and 7.2–8.6 (m, 12, adamantyl protons).

Anal. Calcd for $C_{10}H_{14}Br_2$: C, 40.85; H, 4.80; Br, 54.35. Found: C, 40.42; H, 4.60; Br, 53.91.

4,5-Epoxidoprotoadamantane (Mainly 26).—To a solution of 264 mg (2.0 mmol) of protoadamantene (**19**)[23] in 10 ml of methylene chloride at 0°, 364 mg of 80% *m*-chloroperoxybenzoic acid dissolved in 5 ml of methylene chloride was added carefully. The stirring was continued for 30 min at 0° and then for 2 hr at room temperature. The reaction mixture was extracted with a 5% sodium bisulfite solution, followed by shaking with 5% sodium bicarbonate solution and then water. After drying over anhydrous sodium sulfate, the organic solvent was evaporated in a rotating evaporator, and the resulting residue sublimed *in vacuo* to give 252 mg (85%) of protoadamantyl 4,5-epoxide as a waxy solid, mp 237.5–239.0°. Analytical glpc of this sublimate gave two peaks in the ratio of 6:1 taken to indicate a mixture of the exo and endo epoxides. Attempts to separate the epoxide mixture by silica gel chromatography were not fruitful. Chemical reduction of the epoxide followed by hydrolysis gave products which indicated that exo epoxide **26** was the major component. The nmr spectrum of the sublimate showed a six-line pattern of the epoxide H at τ 6.84 ± 0.25 and 7.25–9.00 (m, 12, protoadamantyl H); its mass spectrum (70 eV) was *m/e* (rel intensity) 150 (46, M^+), 136 (26), 132 (8), 121 (21), 117 (24), 106 (20), 104 (28), 93 (52), 91 (48), 81 (37), 88 (60), 79 (100), and 77 (31).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.21; H, 9.67.

Reduction of 4,5-Epoxidoprotoadamantane (Mainly 26).—To a suspension of 30 mg of lithium aluminum hydride in 5 ml of anhydrous ethyl ether was added 100 mg (0.7 mmol) of epoxide sublimate (above) dissolved in 10 ml of anhydrous ethyl ether. The usual work-up[27] gave 92 mg of a mixture of products. Analytical glc indicated that this mixture consisted of one major product and three minor products. The major component could be separated by chromatography on a silica gel column with benzene–2% ether as eluent. This gave 48 mg (48%) of *exo*-protoadamantan-4-ol.[1n] The structure was established by comparison with an authentic sample by glc coinjection, as well as by the identity of their ir and nmr spectra.

Adamantane-2a,4a-diol (27).—To 300 mg (2 mmol) of the epoxide sublimate (mostly **26**) dissolved in 10 ml of 80% aqueous acetone, 1 drop of concentrated hydrochloric acid was added and the mixture refluxed for 2 hr. The solution was first concentrated *in vacuo* to a small volume (*ca.* 2 ml) and then extracted five times with ether (10 ml each). After drying over anhydrous sodium sulfate and evaporation *in vacuo*, a solid was obtained. Sublimation *in vacuo* gave 265 mg (79%) of adamantane-2a,4a-diol (**27**): mp 305–310° dec; ir 3619 (free) and 3553 cm^{-1} (bonded OH peaks); nmr τ 5.93 (t, 2, CHOH, J = 2.5 Hz, $\Delta\nu_{1/2}$ = 7.5 Hz), 6.5 (broad s, 2, OH, signal disappears when sample is shaken with D_2O), and 7.75–8.67 (m, 12, adamantyl H).

The diol **27** was also prepared for comparison purposes by the lithium aluminum hydride reduction of 4a-hydroxyadamantan-2-one.[11] The identity of the two samples was confirmed by glpc coinjection, and nmr spectra comparison.

***exo*-Protoadamantane-4,5-*cis*-diol (29).**—Toa so lution of 130 mg (1 mmol) of **19** in 5 ml of absolute ether, 250 mg of osmium tetroxide dissolved in 3 ml of absolute ether was added; black osmate **28** precipitated instantaneously. After standing for 2 days at room temperature, evaporation of the solvent gave a black residue. To this 5 ml of pyridine, 5 ml of water, and 250 mg of sodium bisulfite were added, and the resulting mixture was stirred for 1 hr. The mixture was extracted five times with chloroform (10 ml each), and the combined organic layers were washed two times with cold 15% hydrochloric acid, once with saturated potassium bicarbonate solution, and then with water. The solvent was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to give 138 mg (82%) of *exo*-protoadamantane-4,5-*cis*-diol (**29**) as a waxy solid: mp 212–216°; ir $\Delta\nu_{OH}$ 80 cm^{-1}; nmr τ 5.82 (d of d, 1, CHOH, C-4, $J_{4,5}$ = 7.5 Hz, $J_{3,4}$ = 3.5 Hz), 6.06 (d of d, 1, CHOH, C-5, $J_{4,5}$ = 7.5 Hz, $J_{5,6}$ = 1.5 Hz), 6.8 (broad s, 2, OH), 7.2–8.9 (m, 12, protoadamantyl H); mass spectrum (70 eV) *m/e* (rel intensity) 168 (50, M^+), 150 (100), 137 (68), 132 (19), 121 (13), 119 (12), 117 (15), 106 (17), 104 (26), 93 (27), 91 (21), 80 (21), and 79 (34).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.70.

***exo*-Protoadamantane-4,5-*cis*-diol Acetonide (30).**—To 40 mg (0.2 mmol) of **29** dissolved in 5 ml of 80% aqueous acetone, 2 drops of concentrated hydrochloric acid was added, and the mixture refluxed for 2 hr. After evaporation of the solvent to a small volume *in vacuo*, the remaining solution was extracted with ether. The combined ether extract was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The solid residue which resulted was sublimed *in vacuo* to give 32 mg (65%) of *exo*-protoadamantane-4,5-*cis*-diol acetonide (**30**) as needles: mp 39.5–41.0°; ir spectrum showed no OH or C=O bands; nmr τ 5.32 (d of d, 1, CHOH, C-4, $J_{4,5}$ = 7.5 Hz, $J_{3,4}$ = 3.5 Hz), 5.63 (broad d, CHOH, C-5, $J_{4,5}$ = 7.5 Hz), 7.2–8.9 (m, 12, protoadamantyl H), 8.45 (s, 3, CH_3), and 8.61 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 208 (0.5, M^+), 193 (100), 151 (20), 133 (20), 91 (45), and 79 (19).

Acid-Catalyzed Rearrangement of Diol 29.—A solution of 50 mg of **29** in 5 ml of 25% aqueous sulfuric acid was heated at 100° for 1.5 hr. After cooling, ice was added and the reaction product was extracted five times with 10 ml of ether. The usual work-up gave 38 mg of a crude product whose nmr spectrum was identical with that from the authentic diol **27**. Attempted rearrangement of **29** by refluxing in an HCl-catalyzed 50% aqueous ethanol solution was unsuccessful.

Registry No.—*endo*-**3**, 28995-98-4; *exo*-**3**, 28840-89-3; **4**, 28786-69-8; **5**, 28996-01-2; **6**, 28996-02-3; **7**, 28996-03-4; **8**, 26832-19-9; **10**, 28996-05-6; **11**, 29038-91-3; **13**, 28996-06-7; **14**, 29038-92-4; **15**, 28996-07-8; **17**, 26496-36-6; **18**, 28996-09-0; **23**, 28989-82-4; **25**, 19288-33-6; *endo*-**26**, 28989-84-6; *exo*-**26**, 28989-85-7; **27**, 28644-55-5; **29**, 28989-87-9; **30**, 28989-88-0.

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(29) F. W. Van Deursen and A. C. Udding, *Recl. Trav. Chim. Pays-Bas*, **87**, 1243 (1968).

(30) Notation adopted for 2,4-disubstituted adamantanes by G. Snatzke and D. Marquarding, *Chem. Ber.*, **100**, 1710 (1967).

A Biogenetically Patterned Synthesis of (±)-Cherylline

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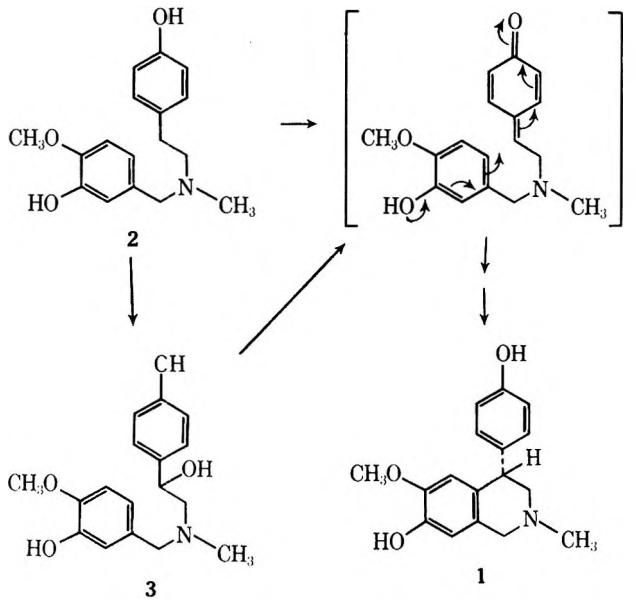
A facile total synthesis of the *Amaryllidaceae* alkaloid cherylline has been achieved *via* base-catalyzed cyclization of *p*-hydroxy-α-{[(3-hydroxy-4-methoxybenzyl)methylamino]methyl}benzyl alcohol (**3**), an intermediate of possible biogenetic significance.

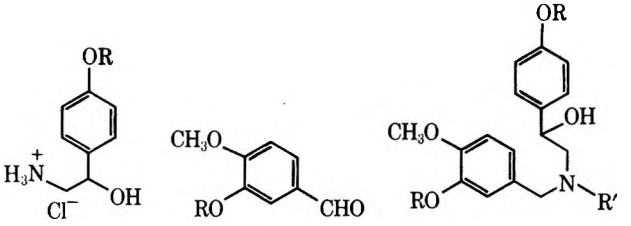
Cherylline, a phenolic 4-phenyltetrahydroisoquinoline alkaloid, has recently been isolated from several *Crinum* species and assigned structure **1**.[2] Although cherylline is unique in structure for an *Amaryllidaceae* alkaloid,[3] its biogenesis likely follows a pathway similar to that operative in the formation of the other alkaloids of this class,[3] *i.e.*, oxidation and cyclization of a suitable derivative of norbelladine. Such a pathway can be envisioned as shown in Scheme I. Direct two-electron

SCHEME I



oxidation of *O,N*-dimethylnorbelladine (**2**) could yield an intermediate quinone methide which subsequently cyclizes to cherylline (**1**); alternatively, hydroxylation of **2** could give the heretofore unknown hydroxy-*O,N*-dimethylnorbelladine **3**, which would yield the same intermediate upon dehydration.[4] Since we had occasion to prepare compounds similar to **3** during the course of other synthetic work, we decided to investigate the feasibility of this scheme as a synthetic route to (±)-cherylline.[5]

(±)-*O*-Benzyloctopamine hydrochloride (**4**) was prepared in 50% yield by lithium aluminum hydride reduction[6] of *p*-benzyloxybenzaldehyde cyanohydrin. Condensation of **4** with *O*-benzylisovanillin[7] (**5**) in alkaline methanol, followed by addition of sodium borohydride and refluxing, gave the secondary amine **6** in 53% yield. N-Methylation of **6** was accomplished in 73% yield by an N-formylation–lithium aluminum hydride reduction sequence. The resulting tertiary amine **7** was subjected to catalytic hydrogenation to give the desired (±)-hydroxy-*O,N*-dimethylnorbelladine **3** in 94% yield.



4, R = benzyl
8, R = H

5, R = benzyl
9, R = H

6, R = benzyl; R′ = H
7, R = benzyl; R′ = CH_3
10, R, R′ = H

With the hypothetical cherylline precursor in hand, cyclization according to Scheme I was then investigated. Treatment of **3** with potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature or at reflux surprisingly led to no reaction; unchanged starting material was recovered in good yield. However, when **3** was refluxed in aqueous ammonium hydroxide solution, the reaction proceeded very smoothly to give (±)-cherylline (**1**) in 79% yield.[8] The synthetic material was indistinguishable from authentic (−)-cherylline[9] in its uv, nmr, and mass spectra as well as in its thin layer chromatographic behavior.[10]

The ease with which **3** could be converted to cherylline proved to be inconvenient at times. When an attempt was made to prepare the hydrochloride of **3** for purposes of elemental analysis, there was obtained after recrystallization (±)-cherylline hydrochloride instead.

(1) This work was supported by Public Health Service Grant CA 10136 from the National Cancer Institute. The high-resolution nuclear magnetic resonance and mass spectrometers used in this investigation were purchased with funds from the National Science Foundation.

(2) A. Brossi, G. Grethe, S. Teitel, W. C. Wildman, and D. T. Bailey, *J. Org. Chem.*, **35**, 1100 (1970).

(3) For a review of the structure, synthesis, and biosynthesis of Amaryllidaceae alkaloids, see W. C. Wildman in "The Alkaloids," Vol. XI, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, pp 308–405.

(4) A third possibility for the biogenesis of cherylline is one involving rearrangement of an 11-hydroxy-5,10b-ethanophenanthridine[3] derivative to a montanine[3]-type skeleton, followed by N-methylation and elimination. Similar laboratory transformations have already been accomplished: Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

(5) For another synthesis of both racemic and natural cherylline, see A. Brossi and S. Teitel, *Tetrahedron Lett.*, 417 (1970); *J. Org. Chem.*, **35**, 3559 (1970).

(6) N. Adityachaudhury and A. Chatterjee, *J. Indian Chem. Soc.*, **36**, 585 (1959).

(7) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 3163 (1931).

(8) For a review of related dihydroxydiarylmethane syntheses, see H. Schnell and H. Krimm, *Angew. Chem., Int. Ed. Engl.*, **2**, 373 (1963).

(9) We thank Dr. A. Brossi for providing us with a very generous sample of natural (−)-cherylline.

(10) Subsequent to this work we learned that various 4-phenyl-substituted tetrahydroisoquinolines have been prepared by Dr. A. Rheiner of F. Hoffmann–La Roche & Co., Basle, Switzerland, by way of acid-catalyzed cyclization of similar precursors (personal communication from Dr. A. Brossi, Hoffmann–La Roche, Inc., Nutley, N. J.).

In order to improve the overall efficiency of the cherylline synthesis, a simpler route to precursor **3** was sought. Consequently, (±)-octopamine hydrochloride (**8**) was reductively condensed with isovanillin (**9**) to afford[11] a 66% yield of the hydroxy-*O*-methylnorbelladine **10**. The phenolic amine **10** was refluxed with ethyl formate in the presence of potassium carbonate and the resulting crude *N*-formyl compound was reduced with lithium aluminum hydride in 1,2-dimethoxyethane. Instead of giving the expected hydroxy-*O*,*N*-dimethylnorbelladine **3**, however, this reaction sequence afforded slightly impure (±)-cherylline (**1**) directly. The racemic alkaloid, obtained in 66% yield from **10**, was probably formed by base-catalyzed cyclization of **3** (or a related salt) during hydrolysis of the hydride–reduction reaction mixture. An nmr spectrum of the crude *N*-formyl intermediate indicated that it had not yet undergone cyclization but rather still retained the norbelladine skeleton. In any event, this three-step sequence of reactions provides an extremely simple and efficient total synthesis of racemic cherylline.[12]

The possible involvement of phenolic amine **3** in the biosynthesis of cherylline will have to be determined by feeding experiments. It is interesting to note in this respect that the related amine **10** could likewise be involved in the biosynthesis of members of the 11-hydroxy-5,10b-ethanophenanthridine[3] class of *Amaryllidaceae* alkaloids. We are currently investigating laboratory syntheses based on this latter hypothesis.

Experimental Section[13]

(±)-α-(Aminomethyl)-*p*-benzyloxybenzyl Alcohol (*O*-Benzyloctopamine) Hydrochloride (4).—A solution of 200 g (1.93 mol) of sodium bisulfite in 300 ml of water was added slowly with stirring to a solution of 84.0 g (0.396 mol) of *p*-benzyloxybenzaldehyde (mp 72–74°) in 300 ml of ethanol–20% tetrahydrofuran. The mixture was stirred at room temperature for 2 hr; the resulting white bisulfite adduct was filtered, rinsed with an ether–20% ethanol mixture, and resuspended in 200 ml of water. To this stirred suspension was slowly added a solution of 60.0 g (1.22 mol) of sodium cyanide in 200 ml of water and the resulting mixture was stirred at room temperature for 12 hr. Extraction with ethyl acetate afforded 90 g (95%) of *p*-benzyloxybenzaldehyde cyanohydrin: ir ($CHCl_3$) 2.80, 2.98 (OH), 4.54 (C≡N), 6.22, 6.64, 8.04, 9.80 μ.

A solution of the crude cyanohydrin (90 g) in 500 ml of tetrahydrofuran was added dropwise to a stirred suspension of 55.0 g (1.45 mol) of lithium aluminum hydride in 2 l. of the same solvent. The reaction mixture was stirred for 12 hr at room temperature and for 1 hr at reflux. The excess hydride was destroyed with saturated aqueous potassium sodium tartrate, *ca.* 10 g of anhydrous sodium sulfate was added, and the mixture was refluxed for 1 hr. The salts were removed by filtration and washed thoroughly with tetrahydrofuran, and the combined filtrates were evaporated to give 78 g of crude solid amine. A solution of the crude amine in an ether–chloroform–ethanol (7:2:1) mixture was cooled to 10° and saturated with dry hydrogen chloride gas with vigorous stirring. The resulting white crystalline salt was isolated by filtration, washed with anhydrous ether, and dried under vacuum to give 53 g (48%) of *O*-benzyloctopamine hydrochloride (**4**), mp 190–195°. Recrystallization from wet acetone–ether afforded pure material, mp 194–196°.

Anal. Calcd for $C_{15}H_{18}ClNO_2$: C, 64.40; H, 6.48; Cl, 12.67; N, 5.01. Found: C, 64.53; H, 6.46; Cl, 12.89; N, 4.80.

Basification of a portion of *O*-benzyloctopamine hydrochloride gave the free amine, mp 101–103°, after recrystallization from aqueous ethanol.

***p*-Benzyloxy-α-{[(3-benzyloxy-4-methoxybenzyl)amino]methyl}benzyl Alcohol (6).**—To a solution of 43.5 g (0.179 mol) of *O*-benzylisovanillin[7] (**5**) and 50.0 g (0.179 mol) of *O*-benzyloctopamine hydrochloride (**4**) in 2.5 l. of absolute ethanol was added 55 g of sodium bicarbonate and the mixture was refluxed with stirring under nitrogen for 2 hr. The solution was cooled with stirring in an ice bath while 10 g (0.26 mol) of sodium borohydride was added in small portions over a period of 30 min and then was refluxed for 2 hr, during which time an additional 10 g of sodium borohydride was added. After evaporation of the ethanol under reduced pressure, the residue was dissolved in dilute hydrochloric acid, neutralized by addition of solid sodium bicarbonate, and extracted thoroughly with ethyl acetate. The resulting crude product was recrystallized from hexane–ethyl acetate to give 45.0 g (53%) of **6**, mp 105–109°. One additional recrystallization afforded pure material: mp 109–111°; ir ($CHCl_3$) 2.76, 2.90, 6.20, 6.62, 8.00 (broad), 8.80, and 9.75 μ; nmr ($CDCl_3$, 90 MHz) δ 2.69 (m, 2, NCH_2), 3.67 (s, 2, $ArCH_2N$), 3.79 (s, 3, OCH_3), 4.68 (dd, 1, J = 5 and 8 Hz, ArCHO), 4.97 (s, 2, benzyl), 5.09 (s, 2, benzyl), 6.67–7.59 (m, 17, aromatic); molecular ion at m/e 469.2258 (calcd for $C_{30}H_{31}NO_4$, 469.2253).

The amine gave a crystalline hydrochloride, mp 166–169° (from wet acetone–ether).

***p*-Benzyloxy-α-{[(3-benzyloxy-4-methoxybenzyl)methylamino]methyl}benzyl Alcohol (7).**—A mixture of 2.00 g (4.26 mmol) of amine **6**, 1.0 g of anhydrous potassium carbonate, and 1.0 g of 3-Å molecular sieves in 50 ml of ethyl formate was refluxed under nitrogen for 12 hr. The reaction mixture was filtered, the residue was washed with absolute ethanol, and the combined filtrates were evaporated under reduced pressure. The resulting white powder was dissolved in tetrahydrofuran, excess lithium aluminum hydride was added, and the mixture was stirred for 4 hr at room temperature and 4 hr at reflux. After decomposition of the excess hydride with saturated aqueous potassium sodium tartrate, removal of the salts by filtration, and evaporation of the solvent, the residue was crystallized from acetone to give 1.50 g (73%) of the tertiary amine **7**: mp 86–88°; ir ($CHCl_3$) 2.76, 2.90 (OH), 6.20, 6.62, 8.10 (broad), and 9.75 μ; nmr ($CDCl_3$, 60 MHz) δ 2.18 (s, 3, NCH_3), 2.44 (m, 2, NCH_2), 3.28, 3.57 (AB pattern, 2, J = 12.5 Hz, $ArCH_2N$), 3.80 (s, 3, OCH_3), 4.58 (dd, 1, J = 4.5 and 9 Hz, ArCHO), 4.96 (s, 2, benzyl), 5.06 (s, 2, benzyl), 6.7–7.4 (m, 17, aromatic); molecular ion at m/e 483.2418 (calcd 483.2409).

Anal. Calcd for $C_{31}H_{33}NO_4$: C, 76.99; H, 6.88; N, 2.90. Found: C, 77.25; H, 7.08; N, 2.64.

***p*-Hydroxy-α-{[(3-hydroxy-4-methoxybenzyl)methylamino]methyl}benzyl Alcohol (3).**—Hydrogen was introduced into a stirred solution of 200 mg (0.414 mmol) of the bisbenzyl ether **7** in 50 ml of absolute ethanol containing 50 mg of 10% palladium on charcoal *via* a gas dispersion tube. After 55 min the catalyst was removed by filtration through Celite 545 and the solvent was evaporated under reduced pressure. The resulting colorless glass was crystallized from ether–hexane to give 118 mg (94%) of the hydroxy-*O*,*N*-dimethylnorbelladine **3**: mp 65–74°, homogeneous to thin layer chromatography (ethyl acetate–chloroform–ethanol, 85:11:4); ir ($CHCl_3$) 2.80, 3.0 (OH), 6.18, 6.27, 8.29, and 9.70 μ; nmr (acetone-d_6, 60 MHz) δ 2.24 (s, 3, NCH_3), 2.48 (m, 2, NCH_2), 3.32, 3.58 (AB pattern, 2, J = 13 Hz, $ArCH_2N$), 3.75 (s, 3, OCH_3), 4.63 (dd, 1, J = 5.5 and 8 Hz, ArCHO), 6.50–7.20 (m, 7, aromatic); mass spectrum (elec-

(11) M. A. Schwartz and R. A. Holton, *J. Amer. Chem. Soc.*, **92**, 1090 (1970).

(12) A reviewer has suggested that both of these routes to cherylline might actually be the result of acid-catalyzed rather than base-catalyzed cyclization; in the first case general acid catalysis by ammonium ion could take place, and in the second case cyclization could occur during acidification of the reaction mixture with hydrochloric acid. We find, however, that cherylline is also produced, although not as cleanly, when **3** is refluxed with 3 mol equiv of sodium hydroxide in water. In addition, the conversion of **10** to cherylline is still successful when the acidification step is replaced by treatment of the reaction mixture with a pH 7 buffer. We therefore feel that the key cyclization step is occurring by base catalysis in this work.

(13) Melting points were measured on a Kofler microscope hot stage and are uncorrected. Infrared and ultraviolet spectra were determined with Perkin-Elmer Model 137 and 202 spectrophotometers, respectively. Nuclear magnetic resonance spectra were measured at 60 MHz with a Varian Associates Model A-60 or at 90 MHz with a Bruker HFX-10 spectrometer. High-resolution mass spectra were obtained using an Associated Electronics Industries MS 902 instrument. Thin layer chromatographies were carried out using silica gel GF. Tetrahydrofuran and dimethoxyethane were purified by distillation from lithium aluminum hydride immediately prior to use. Extracts of reaction products in organic solvents were washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated under reduced pressure using a rotary evaporator. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

tron impact) m/e 285 ($M^+ - H_2O$); mass spectrum (chemical ionization, methane) m/e 304 ($M + H^+$). The compound was too unstable for elemental analysis.

A sample of amine **3** was converted to a hydrochloride, mp 194–230°, by treatment of a solution of it in ethanol–ether with gaseous hydrogen chloride at 0°. Repeated recrystallization of the salt from ethanol–ether gave white crystals, mp 241–243°; the mixture melting point with (±)-cherylline hydrochloride (see below) was undepressed. The amine regenerated upon basification of this salt was identical with cherylline in thin layer chromatographic behavior.

(±)-**Cherylline** (1). **Method A.**—A solution of 120 mg (0.396 mmol) of amine **3** in 50 ml of 4% aqueous ammonia was refluxed for 7 hr. The resulting pale yellow solution was acidified with concentrated hydrochloric acid, neutralized with sodium bicarbonate, and extracted thoroughly with ethyl acetate. The residue obtained upon evaporation of the solvent was crystallized from ether–hexane to give 93 mg (82%) of crude (±)-cherylline, mp 125–200°, identical in thin layer chromatographic behavior with authentic material[9] except for a trace of a polar impurity (ethyl acetate–chloroform–ethanol, 85:11:4). Several recrystallizations from benzene–methanol gave pure (±)-cherylline: mp 209–212° (reported[5] mp 215–216°); identical with (−)-cherylline[9] in tlc, nmr, uv, and mass spectrum; ir (KBr) 2.99, 6.21, 6.29, 6.64, 7.86, 7.98, and 8.91 μ; nmr (acetone-d_6, 60 MHz) δ 2.28 (s, 3), 2.38, 2.82 (ABX pattern, 2, J_{AB} = 11.0 Hz, J_{AX} = 7.5 Hz, J_{BX} = 5.5 Hz), 3.42 (s, 2), 3.52 (s, 3), 3.98 (dd, 1, J = 5.5 and 7.5 Hz), 6.27 (s, 1), 6.45 (s, 1), 6.62, 6.93 (AA'BB' pattern, 4, J = 8.5 Hz); uv max (ethanol) 226 nm (sh, ε 14,000), 280 (3900), 285 (4000), and 295 (sh, 2500); mass spectrum m/e 285, 242, 241, 227, 225, 211, 210, 181.

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.40 H, 6.71; N, 4.69.

A sample of (±)-cherylline was converted to its hydrochloride and recrystallized from ethanol–ether to give 1 HCl, mp 240–243° (the salt first melted at 185°, resolidified at *ca.* 190°, then melted again at the specified temperature).

***p*-Hydroxy-α-{[(3-hydroxy-4-methoxybenzyl)amino]methyl}-benzyl Alcohol (10).**—A mixture of 836 mg (5.50 mmol) of isovanillin[14] (**9**), 1.04 g (5.50 mmol) of (±)-octapamine hydrochloride[14] (**8**), and 500 mg of sodium bicarbonate in 50 ml of methanol was stirred at 50° for 30 min. The reaction mixture was cooled in an ice bath, 1.00 g (26.3 mmol) of sodium borohydride was slowly added, and the resulting solution was stirred at room temperature for 30 min. Most of the solvent was evaporated under reduced pressure; the residue was dissolved in dilute hydrochloric acid, neutralized with sodium bicarbonate, and extracted with ethyl acetate to give 1.05 g (66%) of crude crystalline amine **10**, mp 115–135°. Two recrystallizations from ethyl acetate–methanol afforded the pure compound: mp 150–152°; ir (KBr) 3.0, 6.21, 6.29, 6.64, 7.97, 8.21, and 9.74 μ; nmr (DMSO-d_6, 90 MHz) δ 2.62 (d, 2, J = 6 Hz, NCH_2), 3.67 (s, 2, $ArCH_2N$), 3.74 (s, 3, OCH_3), 4.62 (t, 1, J = 6 Hz, ArCHO), 6.56–7.23 (m, 7, aromatic).

A sample of **10** was treated with excess acetic anhydride in pyridine at −10° to afford the tetraacetyl derivative as a colorless glass.

Anal. Calcd for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06. Found: C, 62.76; H, 6.23; N, 2.79.

(±)-**Cherylline** (1). **Method B.**—To a solution of 100 mg (0.330 mmol) of phenolic amine **10** in 30 ml of ethyl formate–ethanol 3:1 was added 200 mg of potassium carbonate and 1 g of 3-Å molecular sieves. The mixture was refluxed under nitrogen for 8 hr. The solids were filtered and washed with ethanol, and the combined filtrates were evaporated under reduced pressure.

A suspension of the resulting white solid in 1,2-dimethoxyethane was treated with excess lithium aluminum hydride and the mixture was refluxed under nitrogen for 50 hr. The excess hydride was decomposed with saturated aqueous potassium sodium tartrate solution and the resulting suspension was refluxed for 3 hr. The solvent was decanted and the residue was dissolved in dilute hydrochloric acid, neutralized with sodium bicarbonate, and extracted with ethyl acetate. Crystallization of the crude product from ether–hexane afforded 62 mg (66%) of (±)-cherylline (1), identical in all respects with the material prepared by method A above.

Registry No.—**1**, 26996-80-5; **1** HCl, 29002-62-8; **3**, 29002-63-9; **4**, 29002-64-0; **6**, 29002-65-1; **6** HCl, 29002-66-2; **7**, 29038-87-7; **10**, 29002-67-3.

(14) Aldrich Chemical Co., Milwaukee, Wis.

Notes

A New Synthesis of 1,3-Dimethylcytosines

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The discovery of 3-methylcytidine[1] and 1-methyladenosine[2] as minor basic components of nucleic acid stimulated our interest in the chemistry of the iminopyrimidines, which have customarily been made by alkylation of the parent aminopyrimidines. In this note we will describe a new synthesis of 1,3-dimethylcytosine derivatives as a part of the exploitation of our preparative methods of pyrimidine derivatives of the imino type.

Heating of 6-amino-1,3-dimethyluracil (I) with phosphorous oxychloride at 240–250° for 10 hr afforded 6-chloro-1,3-dimethylcytosine (Ia) in 92% yield. The structure of Ia was assigned on the basis of the following evidence. Compound Ia shows a secondary amino stretching absorption band at 3250 cm^{-1} (Nujol). The nuclear magnetic resonance spectrum (CF_3COOH) of Ia shows singlets at 3.73 (CH_3), 3.86 (CH_3), and 6.67 ppm (C_5 H in pyrimidine), and two broad bands at 7.72 and 8.18 ppm ($=N^+H_2$). The mass spectrometry reveals a parent ion (m/e 173) and M + 2 ion, which suggests that one chlorine atom is contained in the molecule. The structure of Ia was finally established by catalytic dechlorination over palladium/carbon to the known 1,3-dimethylcytosine[3-6] (Ib) and by its conversion into the starting material I by treatment with aqueous sodium

(1) (a) R. H. Hall, *Biochem. Biophys. Res. Commun.*, **12**, 36b (1963); (b) R. H. Hall, *Biochemistry*, **4**, 661 (1965).

(2) (a) A. Hampton and D. I. Magrath, *J. Amer. Chem. Soc.*, **79**, 3250 (1957); (b) A. Hampton and M. H. Maguire, *ibid.*, **83**, 150 (1961).

(3) G. H. Hilbert, *ibid.*, **56**, 190 (1934).

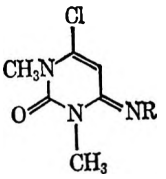
(4) The infrared spectroscopic data of Ib were reported by Angell: C. L. Angell, *J. Chem. Soc.*, 504 (1961).

(5) G. W. Kenner, C. B. Reese, and A. R Todd, *ibid.*, 855 (1955).

(6) P. Brookes and P. D. Lawley, *ibid.*, 1348 (1962).

TABLE I

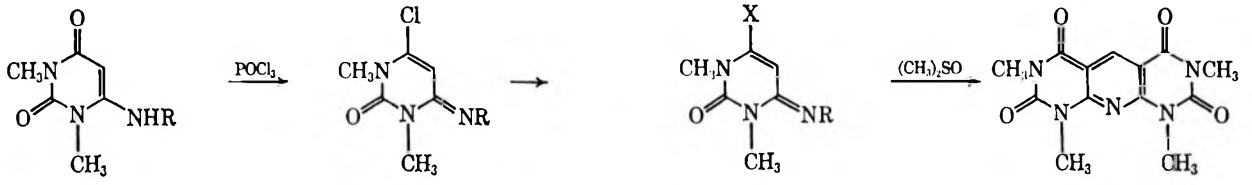
6-CHLORO-1,3-DIMETHYLCYTOSINES



Compd	R	Reaction time, hr	Reaction temp,[a] °C	Purification[b]	Yield, %	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Ia	H	10	250	A[c]	92	150	$C_6H_8ClN_3O$	41.51	4.65	24.20	41.44	4.89	24.02
IIa	n-C_3H_7	5	240	B[d]	43	63	$C_9H_{14}ClN_3O$	50.12	6.54	19.49	50.01	6.35	19.30
IIIa	i-C_3H_7	3	240	B[d]	37	52	$C_9H_{14}ClN_3O$	50.12	6.54	19.49	50.08	6.58	19.68
IVa	C_6H_{11}	3	240	C[e]	92	108	$C_{12}H_{18}ClN_3O$	56.35	7.11	16.43	56.66	6.97	16.44
Va	C_6H_5	5	240	D[d]	88	103	$C_{12}H_{12}ClN_3O$	57.72	4.88	16.97	57.71	4.75	16.82
VIa	$C_6H_5CH_2$	3	240	C[f]	100	81	$C_{13}H_{14}ClN_3O$	59.21	5.35	15.93	59.33	5.36	16.10

[a] Temperature of oil bath. [b] A, recrystallization from chloroform; B, sublimation at 130° (1 mm); C, recrystallization from aqueous ethanol; D, sublimation at 200° (1 mm). [c] Pale yellow prisms. [d] Colorless powder. [e] Colorless prisms. [f] Colorless needles.

SCHEME I



I, R = H
II, R = n-C_3H_7
III, R = i-C_3H_7
IV, R = C_6H_{11}
V, R = C_6H_5
VI, R = $C_6H_5CH_2$

Ia, R = H
IIa, R = n-C_3H_7
IIIa, R = i-C_3H_7
IVa, R = C_6H_{11}
Va, R = C_6H_5
VIa, R = $C_6H_5CH_2$

Ib, R = H; X = H
Ic, R = H; X = NH_2
Id, R = H; X = C_6H_5NH
Ie, R = H; X = CH_3O
If, R = H; X = SH
Ig, R = C_6H_5; X = C_6H_5NH
Ih, R = H; X = SO_3H

bicarbonate. Similarly, heating several 6-(secondary amino)-1,3-dimethyluracils with phosphorous oxychloride gave the corresponding 6-chloro-1,3-dimethylcytosines in good yields (Table I).

The 6-chloro-1,3-dimethylcytosines obtained here served as starting materials for several nucleophilic reactions. For example, displacements of the chlorine in Ia by amino, anilino, alkoxy, and mercapto groups were carried out to yield the respective products. The results of these reactions are summarized in Table II. It is interesting to note that the imino group of 1,3-dimethylcytosines is considerably stable against acid hydrolysis. For example, heating of Ia in concentrated hydrochloric acid at 150–160° for 2 hr gave only a 13% yield of 1,3-dimethylbarbituric acid, with most starting material being recovered.

The reaction of Ia with excess aniline yielded 6-anilino-1,3-dimethyl-4-*N*-phenylcytosine (Ig), which was identical with the product obtained from 6-anilino-1,3-dimethylcytosine (Id) and aniline. 1,3-Dimethyl-6-thiocytosine (If) was also obtained in lower yield by the conventional thiation of I with phosphorous pentasulfide in pyridine. Oxidation of If with hydrogen peroxide in glacial acetic acid gave 1,3-dimethylcytosine-6-sulfonic acid (Ih), whose structure was established by alternative synthesis from Ia and sodium bisulfite. Heating of If in dimethyl sulfoxide gave 1,3,7,9-tetramethyl-2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydropyrido[2,3-*d*:6,5-*d*′]dipyrimidine.[7-9]

Experimental Section[10]

General Procedure for Synthesis of 6-Chloro-1,3-dimethylcytosines (Ia–VIa).—A mixture of 0.1 mol of a 6-amino-1,3-dimethyluracil (I–VI) and 150 ml (1.64 mol) of phosphorous oxychloride was refluxed as described in Table I. After the excess of phosphorous oxychloride was evaporated under reduced pressure, the residue was dissolved in 80 ml of water. The solution was made alkaline with 5% aqueous ammonia, extracted with chloroform (ten 50-ml portions), dried over sodium sulfate, and concentrated to dryness. The residue was recrystallized from an appropriate solvent. When crystals were separated from the alkaline solution, they were collected by filtration, washed with water, dried, and recrystallized from an appropriate solvent.

(7) H. Bredereck, F. Effenberger, and R. Sauter, *Chem. Ber.*, **95**, 2049 (1962).

(8) R. C. Elderfield and M. Wharmby, *J. Org. Chem.*, **32**, 1638 (1967).

(9) K. Senga, F. Yoneda, and S. Nishigaki, *Chem. Pharm. Bull.*, **19**, 215 (1971).

(10) All melting points are uncorrected. Infrared spectra were recorded on a Japan Spectroscopic Co., Ltd., Model IR-E spectrometer; nmr spectra with a Japan Electron Optics Lab. Co., Ltd., Model JNM-C-60-H spectrometer.

TABLE II

REACTION OF 6-CHLORO-1,3-DIMETHYLCYTOSINE WITH SOME NUCLEOPHILES

Compd	R	Reactant (1 equiv)	Reaction time, hr	Temp, °C	Purification[a]	Yield, %	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Ic	NH_2	Excess NH_3 in CH_3OH	8	95	A[b]	56	310	$C_6H_{11}ClN_4O^e$	37.78	5.82	29.38	37.86	5.85	29.47
Id	C_6H_5NH	$C_6H_5NH_2$	3	190	B[c]	83	204	$C_{12}H_{14}N_4O$	62.59	6.13	24.33	62.69	6.10	24.11
Ie	CH_3O	CH_3ONa in CH_3OH	2	Reflux	C[b]	96	156	$C_7H_{11}N_3O_2$	49.69	6.55	24.84	49.86	6.70	25.11
If	SH	Aqueous NaSH	3	Reflux	D[d]	89	260	$C_6H_9N_3OS$	42.09	5.30	24.54	41.87	5.24	24.61

[a] A, recrystallization from a mixture of methanol and acetone; B, recrystallization from aqueous ethanol; C, recrystallization from benzene; D, recrystallization from aqueous dimethyl sulfoxide. [b] Colorless needles. [c] Colorless powder. [d] Pale yellow prisms. [e] Hydrochloride.

1,3-Dimethylcytosine (Ib).—A solution of 3.47 g (0.02 mol) of Ia and 2 ml of concentrated aqueous ammonia in 30 ml of methanol containing 0.3 g of 10% palladium/carbon was hydrogenated at room temperature and at atmospheric pressure. Hydrogenation was stopped when the theoretical volume (448 ml) of hydrogen was consumed. The solution was filtered and evaporated to dryness. The residue was dissolved in 15 ml of water, made alkaline with 5% aqueous ammonia, and extracted with chloroform (five 30-ml portions). The chloroform was dried over sodium sulfate, filtered, and evaporated to dryness to give 1.9 g (68%) of pale yellow powder. Sublimation at 200° (0.5 mm) afforded an analytical sample, mp 143–144°.

Anal. Calcd for $C_6H_9N_3O$: C, 51.78; H, 6.52; N, 30.20. Found: C, 52.07; H, 6.48; N, 29.94.

6-Amino-1,3-dimethylcytosine Hydrochloride (Ic).—A suspension of 1.74 g (0.01 mol) of Ia in 50 ml of saturated methanolic ammonia was heated in sealed tube as described in Table II. After cooling, the reaction mixture was evaporated to dryness. The residue was dissolved in 50 ml of 2 *N* hydrochloric acid with warming. After standing overnight at room temperature, the precipitated crystals were collected by filtration, washed with a small amount of chilled 2 *N* hydrochloric acid, and dried to give 1.0 g of pale yellow needles.

1,3-Dimethyl-6-thiocytosine (If). **A.**—A suspension of 2.6 g (0.015 mol) of Ia and 2.1 g (0.015 mol) of 40% aqueous sodium hydrosulfide in 30 ml of water was heated under the conditions described in Table II. After cooling, the precipitates were collected by filtration, washed with water, and dried to give 2.3 g of pale yellow powder.

B.—A mixture of 0.93 g (0.006 mol) of I and 2.3 g (0.012 mol) of phosphorous pentasulfide in 10 ml of pyridine was refluxed for 5 hr. After evaporating pyridine under reduced pressure, 50 ml of water was added to the resulting residue. The crystals which separated were collected by filtration, washed with water, and dried to give 0.35 g (34%) of If.

6-Anilino-1,3-dimethyl-4-*N*-phenylcytosine (Ig). **A.**—A mixture of 0.87 g (0.005 mol) of Ia, 0.94 g (0.01 mol) of aniline, and 3 drops of concentrated hydrochloric acid was heated at 200° for 3 hr. The reaction mixture was dissolved in 10 ml of ethanol and neutralized with aqueous ammonia. The precipitated crystals were collected by filtration, washed with water, dried, and recrystallized from aqueous ethanol to give 0.8 g (52%) of colorless needles, mp 179–181°.

Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.56; H, 5.92; N, 18.29. Found: C, 70.54; H, 5.82; N, 18.37.

B.—A mixture of 0.5 g (0.002 mol) of 6-anilino-1,3-dimethylcytosine (Id), 0.19 g (0.002 mol) of aniline, and 1 drop of concentrated hydrochloric acid was heated for 1.5 hr at 170°. The reaction mixture was crushed in water, collected by filtration, and washed with water. The crushed mass was recrystallized from aqueous ethanol to give 0.45 g (75%) of pale yellow needles, which was identical with the product obtained in A.

1,3-Dimethylcytosine-6-sulfonic Acid (Ih). **A.**—A suspension of 0.87 g (0.005 mol) of Ia and 1.04 g (0.01 mol) of sodium bisulfite in 10 ml of water was stirred at room temperature for 25 min. The precipitates were collected by filtration, washed with water, and dried. Recrystallization from aqueous dimethyl sulfoxide gave 1.1 g (100%) of colorless powder, mp >360°.

Anal. Calcd for $C_6H_9N_3O_4S$: C, 32.87; H, 4.14; N, 19.17. Found: C, 32.97; H, 4.19; N, 19.37.

B.—To a suspension of 0.68 g (0.004 mol) of If in 5 ml of glacial acetic acid 10 ml of 30% aqueous hydrogen peroxide was added dropwise at room temperature. After being stirred at room temperature for 1.5 hr, the precipitates were collected by filtration, washed with water, and dried to give 0.75 g (85%) of Ih.

1,3,7,9-Tetramethyl-2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydropyrido[2,3-*d*:6,5-*d*′]dipyrimidine.—A suspension of 0.51 g (0.003 mol) of If in 10 ml of dimethyl sulfoxide was refluxed for 5 hr. After cooling, the precipitated crystals were collected by filtration, washed with 50 ml of acetone, and dried to give 0.27 g (60%) of pale yellow crystals.

Registry No.—Ia, 28795-51-9; Ib, 6749-87-7; Ic, 28795-53-1; Id, 28795-54-2; Ie, 28795-55-3; If, 28860-32-4; Ig, 28795-56-4; Ih, 28795-57-5; IIa, 28795-58-6; IIIa, 28795-59-7; IVa, 28795-60-0; Va, 28795-61-1; VIa, 28795-62-2.

Synthesis of 6-Styryl-2-pyrones

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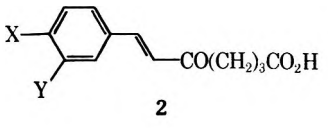
α-Pyrones containing variously oxygenated α′-styryl substituents are known natural products,[1] some of which have been synthesized.[2] We report simple syntheses of five such α-pyrones, three of which (**3a**, **3b**, and **3e**)[1a] proved to be identical with natural substances.[3]

$CH_3CO(CH_2)_3CO_2H$
1

Controlled, base-catalyzed condensations[4] of four aromatic aldehydes with 5-oxohexanoic acid (**1**) yielded 6-arylidene-5-oxohexanoic acids **2a–2d** whose treatment with acetic anhydride in the presence of sodium acetate afforded enol lactones. Dehydrogenation of the latter over palladium on charcoal gave the desired α-pyrones **3a–3d**.



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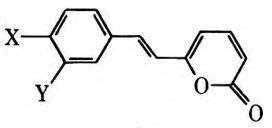

3

a, X = Y = H
b, X+Y = CH_2O_2
c, X = Y = MeO
d, X = $C_6H_5CH_2O$; Y = MeO
e, X = HO; Y = MeO

Since neither vanillin nor its *O*-acetyl or *O*-tetrahydropyranyl derivatives could be condensed with ketone **1** in the above manner, the α-pyrone **3e** related to vanillin was produced by acid-catalyzed debenzylation of **3d**.

Experimental Section[5]

6-Arylidene-5-oxohexanoic Acids (**2a–2d**).—The required aldehyde (1 equiv) was condensed with 5-oxohexanoic acid (1 equiv) in the presence of alcoholic NaOH solution (5% 2 equiv) by heating on a water bath (80°) for 20–30 min and a work-up according to Erlenmeyer.[4] Crystallization from an appropriate solvent afforded the desired product in 40–60% yield.

2a: light yellow crystals from EtOH; mp 114–116°; ir 3509–2638, 1715, 1661, 1618, 982 cm^{-1}; nmr δ 1.8–2.2 (m, 2, CH_2 at 3), 2.3–2.9 (m, 4, CH_2 at 2 and 4), 6.7 (d, 1, J = 16 Hz, HC=C), 7.2–7.7 (m, 6, HC=C and Ph), 10.0 (s, 1, COOH).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.27; H, 5.92.

2b: recrystallized from benzene as yellow crystals; mp 139–141°; nmr δ 5.98 (s, 2, CH_2O_2).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.82; H, 5.21.

2c: yellow crystals from benzene; mp 105–107°; nmr δ 3.92 (s, 6, 3′,4′-OCH_3).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.68; H, 6.72.

2d: yellow crystals from benzene; mp 129–131°; nmr δ 3.9 (s, 3, OCH_3), 5.2 (s, 2, $ArCH_2O$).

Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.09; H, 6.09.

6-Styryl-2-pyrones (**3a–3e**).—The above keto acids (**2a–2d**) were refluxed 6 hr in acetic anhydride containing a catalytic amount of fused sodium acetate. Removal of acetic anhydride and sodium acetate and recrystallization from a suitable solvent afforded the desired enol lactone. Some enol lactones were unstable on standing and were immediately dehydrogenated by refluxing (15 hr) in xylene containing a catalytic amount of Pd/C (10%). The product was directly chromatographed on a silica gel (E. Merck) column and eluted with $CHCl_3$. Recrystallization of the appropriate fraction from a suitable solvent afforded the desired α-pyrone. Synthetic **3a**, **3b**, **3c**, and **3e** had ir and nmr spectra identical with those of authentic samples[1a,3] and suffered no mixture melting point depression.

3a.—Keto acid **2a** (2.4 g) on enol-lactonization and recrystallization of the product from petroleum ether gave an enol lactone (1.9 g): yellow crystals; mp 108–110°; ir 1751, 1661, 1592, 971 cm^{-1}. Dehydrogenation of 0.35 g thereof and purification of the product as described above gave **3a** (0.15 g) as yellow crystals from petroleum ether: mp 113–114°; ir 1733, 1637, 1603, 972 cm^{-1}; nmr δ 6.1–6.3 (m, 2, pyronic), 6.60 (d, 1, J = 16 Hz, C=CH), 7.2–7.6 (m, 7, aromatic, pyronic and C=CH).

3b.—Similarly, keto acid **2b** (0.42 g) gave an enol lactone (0.3 g), yellow crystals from benzene, mp 131–133°, which on dehydrogenation, purification, and recrystallization of the product from benzene yielded **3b** (0.17 g) as yellow crystals: mp 173–174°; nmr δ 6.0 (s, 2, O_2CH_2).

3c.—Similarly the enol lactone (0.27 g, mp 92–95°) from the keto acid **2c** (0.31 g) furnished **3c** (0.15 g): yellow crystals from petroleum ether; mp 96–98°, nmr δ 3.93 (s, 6, OCH_3 at 3′ and 4′).

3d.—Enol lactone (2.0 g, mp 130–132°) from keto acid **2d** (2.5 g) afforded **3d** (1.2 g) as yellow crystals from EtOH: mp 131–133°; nmr δ 3.9 (s, 3, OCH_2Ar).

Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.56; H, 5.40.

3e.—α-Pyrone **3d** (1.2 g) was debenzylated with 48% HBr (0.1 ml) in AcOH (5 ml) by heating on a steam bath for 10 min. After neutralization with a saturated solution of sodium bicarbonate and extraction with chloroform, the crude product was purified as in the previous cases. The final product **3e** was obtained as yellow crystals (0.3 g) from benzene: mp 158–160°; ir 3360 cm^{-1} (OH); nmr δ 3.9 (s, 3, OCH_3), 5.9 (s, 1, OH).

Registry No.—**2a**, 28845-58-1; **2b**, 28845-59-2; **2c**, 28845-60-5; **2d**, 28845-61-6; **3a**, 1208-97-5; **3b**, 1219-50-7; **3c**, 28845-64-9; **3d**, 28845-65-0; **3e**, 1429-09-0.

(1) (a) O. R. Gottlieb, A. M. Bittencourt, W. B. Mors, and M. T. Magalhães, *Ann. Acad. Brasil Cienc.*, **36**, 29 (1964); (b) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, pp 82–134.

(2) J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 502 (1960); D. G. F. R. Kostermans, *Recl. Trav. Chim. Pays-Bas*, **70**, 79 (1951); L. P. Sorokina and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1**, 73 (1964) [*Chem. Abstr.*, **60**, 9233 (1964)].

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(5) Melting points are uncorrected. Infrared spectra were recorded as KBr pellets on a Perkin-Elmer Model 137 spectrometer. Nmr spectra were run in $CDCl_3$ on a Varian A-60D spectrometer. The petroleum ether used had a boiling point range of 80–100°.

Preparation and Nuclear Magnetic Resonance Spectra of 11-Oxygenated Estrogen Catechols[1]

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A distinctive feature of the nmr spectrum of 2-hydroxyestrone Ia is the two aromatic proton absorptions

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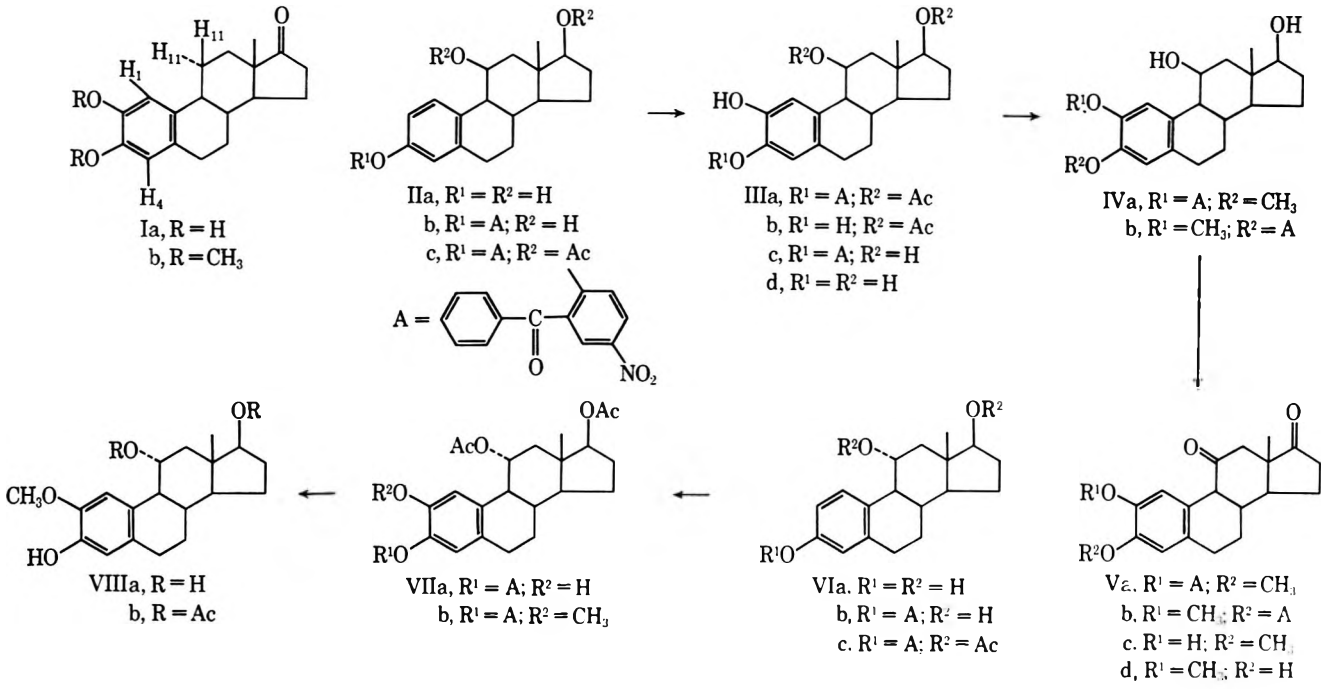
SCHEME I



in the downfield region. The H-1 and H-4 protons appear as singlets 12 Hz apart with that of H-1 being the downfield one.[3] Inspection of the spectra of the parent compound and of its various derivatives[4] revealed that the H-1 resonance was consistently of lower intensity and greater half-height width than that of the corresponding H-4 resonance. This difference persisted in the presence of identical substituents at C-2 and C-3, and its origin must therefore reside in long-range coupling with protons elsewhere in the molecule. The most likely candidates for this interaction are the benzylic[5] hydrogens at C-6 and C-9. One might infer that, contrary to the observed result, H-4 would have greater opportunity for benzylic coupling with the two protons at C-6 than H-1 with the single hydrogen at C-9. It is possible, however, that the conformationally rigid H-9 has an angular relationship to H-1 more favorable for coupling than that of the hydrogens on the flexible C-6 to H-4. To establish whether benzylic coupling was responsible for the broadening of the H-1 resonance, the benzylic hydrogens at C-6 and C-9 in 2,3-dimethoxyestrone Ib were exchanged for deuterium,[6] and the replacement was confirmed by the absence of benzylic proton resonance at δ 2.63 in the deuterated compound. The spectrum of the deuterated compound, however, still retained the full difference of 0.5 Hz between the half-height widths of the H-1 and H-4 bands which eliminated the benzylic protons as being responsible for this interaction. The proximity of the hydrogens on C-11 to the affected H-1 proton suggested these protons as the next logical candidates for long-range coupling with H-1. To investigate this possibility it was necessary to prepare the 11-oxygenated derivatives of 2-hydroxy estrogens and to obtain their nmr spectra. Furthermore, 2-hydroxylation is the major metabolic pathway of estradiol in man,[7] which together with the biological significance of 11-hydroxylation makes the preparation of compounds containing both these features of considerable interest.

The synthesis of 2,11-dihydroxy estrogens presents the choice of introducing the C-2 hydroxy group prior to that at C-11 or adding it to the preformed 11-hydroxy estrogen. For obvious reasons of starting material availability and synthetic ease we selected the latter sequence. Reductive aromatization[8] of 11β-hydroxyandrost-1,4-dien-3,17-dione by a modification of the published procedure[9] gave 11β-hydroxyestradiol IIa. The epimeric 11α-hydroxy compound was not available by this method since reductive aromatization in this instance results in ring C cleavage.[9] The method of Tsuda, *et al.*,[10] was, therefore, used to prepare 11α-hydroxyestradiol VIa.

The introduction of the C-2 hydroxy group in both epimeric 11-hydroxyestradiols was accomplished by an application of the procedures used in the original catechol estrogen synthesis.[11] Condensation with 2-chloro-5-nitrobenzophenone, cyclization, and oxidation of the resultant aromatic ether gave the 2-hydroxy compounds which were converted to the various derivatives as depicted in Scheme I. Smiles rearrangement of the intermediate catechol ether permitted the preparation of isomeric 2- and 3-monomethyl compounds, while oxidation of the protected intermediates led to the 11-keto derivatives.

Nmr Spectra.—Inspection of the aromatic resonances in the various compounds showed that the difference in the half-height widths between the H-1 and H-4 resonances was retained in all except the 11α-hydroxy

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(9) J. S. Baran, *J. Med. Chem.*, **10**, 1188 (1967).

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(11) J. Fishman, *J. Amer. Chem. Soc.*, **80**, 1213 (1958).

and 11-keto derivatives. This clearly pointed to the 11α H as the proton responsible for the long-range coupling of H-1. That this was the case was confirmed by a double resonance experiment on the 11β-hydroxy derivative, where the H-1 and H-4 resonances had half-height widths of 2.8 and 2.0 Hz, respectively. Irradiation at δ 4.40, the absorption frequency of the 11α hydrogen, resulted in a disappearance of the inequality of H-1 and H-4 resonances with both now being 2 Hz wide at half-height. It should be emphasized that the difference in the height of H-1 and H-4 is not derived from a nuclear Overhauser effect[12,13] since in repeated integrations the areas of H-1 and H-4 resonances were equal. The steric relationship of the protons involved in this homobenzylic interaction permits some observations on its mechanism. In cases where unsaturation is present in the coupling path, a mechanism involving electron overlap is the preferred one.[14] In the present case the protons best situated for overlap of their σ bonds with the π electrons of the benzene ring are located at 9α and 11β positions. The fact that the 11α hydrogen, which is closest in space to H-1 (<3 Å)[15] but which is poorly situated for electron overlap is involved in the coupling, suggests that this interaction proceeds by a direct through-space mechanism.[16]

In view of the proximity of the two centers the effect of substitution at C-11 on the chemical shift of H-1 is of interest. Inspection of the chemical shift values of H-1 in the various structures listed in Table I reveals

TABLE I

CHEMICAL SHIFTS OF AROMATIC PROTONS IN 11-SUBSTITUTED 2,3-DIHYDROXYESTRATRIENES

C-11	H-1	H-4	ΔH-1	ΔH-4
<H, H	6.88	6.67		
<H, OAc	6.67	6.67	−0.21	0
<OAc, H	6.67	6.70	−0.11	+0.03
=O	6.60	6.64	−0.28	−0.03
<H, H[a]	6.68	6.47		
<H, OH[a]	6.77	6.53	+0.11	+0.06
<OH, H[a]	7.58	6.43	−0.90	−0.1

[a] In DMSO-d_6; all others in $CDCl_3$.

that the 11α and 11β acetates produce only a small upfield shift with little difference between the epimers. The 11-ketone also results in a modest upfield shift suggesting the influence of its shielding cone although clearly not at its maximal zone. The 11α- and 11β-hydroxy derivatives in dimethyl sulfoxide both produce downfield shifts with that of 11α hydroxyl being ten times greater. This large deshielding is clearly the result not of the 11α-hydroxyl group itself but of the hydrogen-bonded dimethyl sulfoxide molecule. The geometry of the hydrogen-bonded hydroxy–dimethyl sulfoxide complex is speculative,[17] but clearly the orientation of the 11α-hydroxy group allows for greater proximity of the electropositive sulfur to H-1. This distance-related dimethyl sulfoxide effect may prove useful in other similar situations as an aid in structure determination.

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(16) C. N. Banwell and N. Sheppard, *Discuss. Faraday Soc.*, **34**, 115 (1962).

Experimental Section[18]

Estra-1,3,5(10)-triene-3,11β,17β-triol 3-(2-Benzoyl-4-nitro)phenyl Ether (IIb).—To a solution of 0.42 g of estra-1,3,5(10)-triene-3,11β,17β-triol (IIa) and 0.05 g potassium hydroxide in 40 ml of 95% ethanol, 0.35 g of 2-chloro-5-nitrobenzophenone was added. The reaction mixture was refluxed for 48 hr. After concentration to one-half volume, the cooled mixture was poured into 1 *N* sodium hydroxide solution and extracted with chloroform. Removal of the solvent yielded 0.54 g of a yellow oil which was chromatographed on alumina. Elution with petroleum ether (bp 30–60°)–benzene (1:1) yielded 0.04 g of 2-ethoxy-5-nitrobenzophenone while benzene and chloroform–benzene (1:1) gave 0.42 g of estra-1,3,5(10)-triene-3,11β,17β-triol 3-(2-benzoyl-4-nitro)phenyl ether (IIb) which crystallized from methanol–water, mp 123–125°, $[\alpha]^{27}D$ +74.2°.

Anal. Calcd for $C_{31}H_{31}NO_6 \cdot H_2O$: C, 70.04; H, 6.26. Found: C, 69.85; H, 6.02.

The diacetate IIc, obtained with acetic anhydride in pyridine, crystallized from ether, mp 108–110°, $[\alpha]^{27}D$ +3.15°.

Anal. Calcd for $C_{35}H_{35}NO_8$: C, 70.33; H, 5.90. Found: C, 70.15; H, 5.85.

Estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 3-(2-Benzoyl-4-nitro)phenyl Ether 11,17-Diacetate (IIIa).—To a solution of 0.33 g of the diacetate IIc in 1 ml of glacial acetic acid 1 ml of concentrated sulfuric acid was added slowly with cooling and stirring. The dark red solution was stored at room temperature for 30 min and then diluted with 3.5 ml of glacial acetic acid, and 1 ml of 30% hydrogen peroxide was added dropwise with stirring. After 5 min the color of the solution lightened and after standing for 30 min at room temperature it was poured into ice–water and the precipitate filtered off. After washing with 5% sodium bicarbonate solution and then water, the precipitate was dried and recrystallized from methanol–water to give 0.2 g of IIIa, mp 134–136°, $[\alpha]^{27}D$ +36.5°.

Anal. Calcd for $C_{35}H_{35}NO_9 \cdot {}^1/_2H_2O$: C, 67.41; H, 5.78. Found: C, 67.25; H, 5.78.

Estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 11,17-Diacetate (IIIb).—A sample of IIIa (0.08 g) was refluxed for 2 hr in 10 ml of piperidine. The dark solution was diluted with benzene and washed with dilute sulfuric acid and then water. Evaporation of solvent and crystallization from methanol yielded 0.02 g of IIIb: mp 220–224°; $[\alpha]^{28}D$ +36.7°; nmr 1.11 (s, C-18 CH_3), 1.90 (s, 11β-CH_3CO), 5.77 (m, H-11α), and 6.63 (s, H-1,4).

Anal. Calcd for $C_{22}H_{28}O_6 \cdot CH_3OH$: C, 65.69; H, 7.67. Found: C, 65.63; H, 7.61.

Estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 3-(2-Benzoyl-4-nitro)phenyl Ether (IIIc).—A solution of 0.1 g of IIIa in 20 ml of methanol containing 1 ml of concentrated sulfuric acid was refluxed for 15 hr. The solution was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate, dried, and evaporated to give material which crystallized from dilute methanol to give 0.07 g of IIIc, mp 212–214°, $[\alpha]^{27}D$ +79.6°.

Anal. Calcd for $C_{31}H_{31}NO_7 \cdot CH_3OH$: C, 68.43; H, 6.28. Found: C, 68.58; H, 6.22.

Estra-1,3,5(10)-triene-2,3,11β,17β-tetrol (IIId).—A solution of 80 mg of IIb in 20 ml of tetrahydrofuran was stirred with 70 mg of $LiAlH_4$ for 4 hr. The reaction mixture was diluted with 20 ml of acetone and then acidified with dilute HCl. After extraction with ethyl acetate the organic layer was washed with sodium bicarbonate solution and then water, dried, and evaporated. The residue was crystallized from acetone–petroleum ether to give 24 mg of IIId: mp 231–232° with previous melting and solidification; nmr (DMSO) 0.89 (C-18 CH_3), 4.40 (H-11α),

(17) R. J. Oulette, D. L. Marks, and D. Miller, *J. Amer. Chem. Soc.*, **89**, 913 (1967).
(18) Rotations were carried out on chloroform unless otherwise specified. Melting points were obtained on a hot stage apparatus and are corrected. Nmr spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. The chemical shifts are reported in δ (parts per million) and the couplings are given in hertz. The double resonance experiment was performed on a Varian V-6058A spin decoupler.

6.38 (H-4), and 6.63 (H-1). Irradiation at δ 4.40 reduced the H-1 and H-4 resonances to equal width at half-height.

Anal. Calcd for $C_{18}H_{24}O_4 \cdot H_2O$: C, 67.06; H, 8.13. Found: C, 67.42; H, 7.94.

Smiles Rearrangement and O-Methylation of IIIc.—A solution of 160 mg of IIIc in 10 ml of Claisen alkali was allowed to stand for 10 min, acidified, and extracted with chloroform to give a partially rearranged product. The rearranged mixture was dissolved in 10 ml of tetrahydrofuran and stored for 24 hr at 5° with excess ethereal diazomethane. Evaporation of excess reagent and solvent gave a material which upon preparative thin layer chromatography in cyclohexane–ethyl acetate (1:1) gave 60 mg of a more polar compound identified as estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 2-(2-benzoyl-4-nitro)phenyl ether 3-methyl ether (IVa) [nmr 3.70 (s, 3-OCH_3), 4.73 (m, H-11α)] and 28 mg of a less polar material identified as the isomeric 2-methyl ether 3-(2-benzoyl-4-nitro)phenyl ether IVb [nmr 3.66 (s, 2-OCH_3), 4.55 (m, H-11α)]. Neither of the two compounds could be obtained crystalline.

2,3-Dihydroxyestra-1,3,5(10)-triene-11,17-dione 3-Methyl Ether (Vc).—To a solution of 30 mg of IVa in 10 ml of acetone Jones reagent was added dropwise until the orange-brown color persisted. The mixture was allowed to stand for 20 min at room temperature, poured into water, and extracted with chloroform. Following evaporation of the solvent, the noncrystalline product Va was homogeneous according to thin layer chromatography in cyclohexane–ethyl acetate (1:1). A solution of the above oil in piperidine was refluxed for 2 hr and cooled, benzene was added, and the reaction mixture was washed well with 5% sulfuric acid. Drying and evaporation of solvent gave 8 mg of a semisolid Vc which crystallized from methanol: mp 135–140°; $[\alpha]D$ +129.7°; nmr 0.93 (s, C-18 CH_3), 3.86 (s, 3-OCH_3), 6.57 (s, H-1), and 6.62 (s, H-4).

Anal. Calcd for $C_{19}H_{22}O_4 \cdot CH_3OH$: C, 69.34; H, 7.57. Found: C, 68.91; H, 6.98.

2,3-Dihydroxyestra-1,3,5(10)-triene-11,17-dione 2-Methyl Ether (Vd).—This isomer was prepared from 14 mg of IVb exactly as described above: mp 145–147°; $[\alpha]D$ +123.1°; nmr 0.93 (s, C-18 CH_3), 3.78 (s, 2-OCH_3), 6.44 (s, H-1), and 6.70 (s, H-4).

Anal. Calcd for $C_{19}H_{22}O_4 \cdot CH_3OH$: C, 69.34; H, 7.57. Found: C, 68.86; H, 7.72.

Estra-1,3,5(10)-triene-3,11α,17β-triol 3-(2-Benzoyl-4-nitro)-phenyl Ether 11,17-Diacetate (VIc).—The diacetate VIc was prepared from VIa as described for IIc and gave a crystalline product from ether, mp 103–105°, $[\alpha]D$ −66.0°.

Anal. Calcd for $C_{35}H_{33}O_8N$: C, 68.63; H, 7.51. Found: C, 68.48; H, 7.24.

Estra-1,3,5(10)-triene-2,3,11α,17β-tetrol 2-Methyl Ether 11α,-17β-Diacetate (VIIIb).—A 0.745-g sample of VIc was converted to the 2-hydroxy derivative VIIa which without purification was methylated with diazomethane to VIIb. The latter, upon cleavage with piperidine, afforded 0.23 g of VIIIb. The above reactions were carried out by procedures identical with those used in the 11β-hydroxy series. The isolated VIIIb crystallized from acetone–petroleum ether, mp 226–228°, $[\alpha]D$ −101.7°.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.42; H, 7.83.

Estra-1,3,5(10)-triene-2,3,11α,17β-tetrol 2-Methyl Ether (VIIIa).—A solution of 0.1 g of VIIIb in 20 ml of methanol containing 1 ml of concentrated sulfuric acid was refluxed for 15 hr. The solution was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate, dried, and evaporated to give the 0.06 g of VIIIa: crystallized from dilute methanol; mp 243–245°; $[\alpha]D$ +25.8°; nmr 0.78 (s, C-18 CH_3), 3.85 (s, 2-OCH_3), 6.67 (s, H-4), and 7.76 (s, H-1).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.19; H, 7.98.

2,3-Dimethoxyestra-1,3,5(10)-trien-17-one-6α,6β,9α-d_3.—A solution of 50 mg of 2,3-dimethoxyestra-1,3,5(10)-trien-17-one (Ib) in 20 ml of ethyl acetate was shaken with deuterium over 100 mg of 10% palladized charcoal for 4 hr at room temperature and atmospheric pressure. Filtration of the catalyst and evaporation of solvent gave the trideuterio derivative of Ib. The nmr spectrum of the starting material Ib showed a three-proton multiplet at 2.53 representing the benzylic hydrogens, and 1-proton singlet at 6.83 and 6.63 with the former being 0.6 Hz wider at half-height. The deuterated product lacked the absorption at 2.63 but the resonances at 6.83 and 6.63 were unchanged in shape.

Registry No.—IIb, 28841-14-7; IIc, 28841-15-8; IIIa, 28897-65-6; IIIb, 28897-66-7; IIIc, 28897-67-8; IIId, 28897-68-9; IVa, 28897-69-0; IVb, 28841-16-9; Vc, 28897-70-3; Vd, 28897-71-4; VIc, 28897-72-5; VIIIa, 28897-73-6; VIIIb, 28897-74-7; 2,3-dimethoxyestra-1,3,5(10)-trien-17-one-6α,6β,9α-d_3, 28897-75-8.

New Approaches to the Preparation of Halogenated Methylenediphosphonates, Phosphonoacetates, and Malonates

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Three synthetic routes to tetraalkyl dihalomethylenediphosphonates have appeared in the literature. Low yields of tetraethyl dichloromethylenediphosphonate were obtained from the reaction of Cl_3CBr and $P(OC_2H_5)_3$.[1] This is not a useful preparative method, however, as there are a number of products and separation is difficult. Reaction of molecular halogen with the sodium carbanion of tetraisopropyl methylenediphosphonate gave mixtures containing less than 50% of the dihalo derivative.[2] Again, separation problems render this method impractical for preparative purposes. Equation 1 describes the halogenation *via* hypohalite

$$2NaOX + H_2C(PO_3R_2)_2 \longrightarrow X_2C(PO_3R_2)_2 + 2NaOH \quad (1)$$
$$X = Cl, Br, I$$

reaction with tetraalkyl methylenediphosphonate.[2] Quantitative yields of $X_2C(PO_3R_2)_2$ are obtained when X = Cl or Br; when X = I, the product is somewhat unstable resulting in reduced yields.

Each of the above three methods could conceivably be modified to yield tetraalkyl monohalomethylenediphosphonates. Chloroform reacts with trialkyl phosphite in a complex manner; the intermediacy of $ClCH(PO_3R_2)_2$ has been postulated but never proven.[3] Direct halogenation and hypohalite halogenation have both been shown to yield at best mixtures of tetraalkyl monohalomethylenediphosphonate with the corresponding unhalogenated and dihalogenated derivatives.[2] These mixtures are exceedingly difficult to separate, rendering pure tetraalkyl monohalomethylenediphosphonates nearly inaccessible.[4]

Hata[5] has reported the preparation of monobromo derivatives of activated methylenes through the reaction of equimolar quantities of the corresponding di- and unhalogenated species. This method was not successful with diphosphonates. After extended heating (100°) of a mixture of tetraisopropyl dibromomethylenediphosphonate and tetraisopropyl methylenediphos-

(1) P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 2953 (1962).

(2) O. T. Quimby, J. D. Curry, D. A. Nicholson, J. B. Prentice, and C. H. Roy, *J. Organometal. Chem.*, **13**, 199 (1968).

(3) A. J. Burn, J. I. G. Cadogen, and P. J. Bunyan, *J. Chem. Soc.*, 4369 (1964).

(4) O. T. Quimby, J. B. Prentice, and D. A. Nicholson, *J. Org. Chem.*, **32**, 4111 (1967).

(5) T. Hata, *Bull. Chem. Soc. Jap.*, **37**, 547 (1964).

phonate, no change in composition could be detected by ^{31}P nmr.

Accordingly, a goal of our research became the discovery of a method for the synthesis of tetraalkyl monohalomethylenediphosphonates in high purity and high yield. This goal was realized during a study of the properties of tetraalkyl dihalomethylenediphosphonates.

Reaction of sodium sulfide and tetraisopropyl dichloromethylenediphosphonate produced compound I in 25–50% yield (eq 2). Although the mechanism of the reaction is not clear, it is obvious that both nucleophilic displacement and reduction are involved.

$$2Na_2S + 2Cl_2C[PO_3(i\text{-}C_3H_7)_2]_2 \longrightarrow [(i\text{-}C_3H_7)_2O_3P]_2CHSSCH[PO_3(i\text{-}C_3H_7)_2]_2 + 4NaCl \quad (2)$$

When sodium hydrosulfide was employed in reaction 2 in place of Na_2S, an immediate precipitate of sulfur was observed upon addition of the first portion of NaSH. Following the addition of 1 equiv of NaSH to 1 equiv of the dichloromethylenediphosphonate, nearly quantitative yields of elemental sulfur and tetraisopropyl chloromethylenediphosphonate were isolated, as described in eq 3. Addition of a second equivalent of

$$NaSH + R_2O_3PCPO_3R_2 \longrightarrow NaX + \downarrow S + R_2O_3PCPO_3R_2 \quad (3)$$

NaSH resulted in reduction of the second halogen to form the methylenediphosphonate (eq 4).

$$NaSH + R_2O_3PCPO_3R_2 \longrightarrow NaX + S\downarrow + R_2O_3PCPO_3R_2 \quad (4)$$

Table I describes the variation in yield of monohalomethylenediphosphonates with reaction temperature

TABLE I
REDUCTION OF TETRAALKYL DIHALOMETHYLENEDIPHOSPHONATES WITH SODIUM HYDROSULFIDE

—$R_2O_3PCX_2PO_3R_2$— R	X	Reaction temp, °C	Yield of $R_2O_3PCH(X)PO_3R_2$,[a] %
i-C_3H_7	Cl	25	94
i-C_3H_7	Cl	0	84
i-C_3H_7	Br	25	77
i-C_3H_7	Br	0	95
C_2H_5	Cl	25	49
C_2H_5	Cl	0	91
C_2H_5	Br	25	51
C_2H_5	Br	−10	78
C_2H_5	Br	−25	82

[a] Per cent yields were obtained from electronic integration of a ^{31}P nmr spectrum. Reaction conditions were identical except for the variation in temperature. See Experimental Section for details.

where the alkyl groups are ethyl and isopropyl and the halogens are chlorine and bromine. In general, it can be concluded that to obtain maximum yields a lower reaction temperature must be employed for ethyl esters than for isopropyl esters and for bromo derivatives than for chloro derivatives.

The ability of other reducing agents to convert dihalomethylenediphosphonates to monohalomethylenediphosphonates was briefly explored. The results of these experiments are collected in Table II. As can

TABLE II
MISCELLANEOUS REDUCTIONS OF DIHALOMETHYLENEDIPHOSPHONATES

Reducing agent	—$R_2O_3PCX_2PO_3R_2$— R	X	% $R_2O_3PCH(X)PO_3R_2$[a]
NaCN + NaOH	C_2H_5	Br	54
$SnCl_2$	C_2H_5	Br	84
NaCN + NaOH	C_2H_5	Cl	53
$(C_2H_5)_3SiH$	*i*-C_3H_7	Cl	Low[c,d]
Na_2SO_3[b]	*i*-C_3H_7	Cl	54

[a] Reactions were run in aqueous methanol at 25°. Equimolar quantities of reagents were employed. Yields were determined by electronic integration of a ^{31}P nmr spectrum. [b] Sodium bicarbonate was added to buffer the solution. [c] A ^{31}P nmr spectrum of the reaction mixture indicated ~5% reaction. [d] Benzene was employed in place of water as solvent for this reaction.

be seen none of these materials was found to be superior to NaSH with the possible exception of $SnCl_2$. In the reduction of tetraethyl dibromomethylenediphosphonate, subzero reaction temperatures were required with NaSH to achieve yields comparable to those obtained with $SnCl_2$ at 25°.

Extension of this synthetic method to other related systems was briefly examined. Table III records the results of the interaction of dihalomalonates and dihalophosphonoacetates with various reducing agents. High yields of monohalo derivatives could be obtained with the proper reducing agent in all cases examined. Triethyl bromophosphonoacetate was not further purified as we were not able to separate it from the dibromo starting material by vacuum distillation.

In the preparation of dihalomalonates and dihalophosphonoacetates it was found convenient to employ a hypohalite halogenation procedure.[2] Purified yields of triethyl dihalophosphonoacetates and diethyl dihalomalonates ranged from 60 to 80%. This halogenation procedure appeared to be superior to reported methods.[6-8] Halogenation of salts of malonic acid by hypohalites has been reported[9] and Bell, *et al.*,[10] have suggested participation of OBr^- bromination when this ion was present as a catalyst for Br_2 bromination of diethyl malonate.

Experimental Section

Melting and boiling points reported herein are uncorrected. Elemental analyses were carried out in these laboratories. The

(6) N. V. de Bataafsche Petroleum Maatschappij, British Patent 692,261 (June 3, 1953); *Chem. Abstr.*, **48**, 10052*i* (1954).
(7) N. P. Buu-Hoi and P. Demerseman, *J. Org. Chem.*, **18**, 649 (1953).
(8) B. Teichmann, *Acta Chim. Acad. Sci. Hung.*, **41**, 435 (1964); *Chem. Abstr.*, **62**, 6389*h* (1965).
(9) F. Straus and R. Kühnel, *Ber.*, **66**, 1834 (1933).
(10) R. P. Bell, D. H. Everett, and H. C. Longuet-Higgins, *Proc. Roy. Soc., Ser. A*, **186**, 443 (1946).

TABLE III

REDUCTION OF DIHALOPHOSPHONOACETATES AND DIHALOMALONATES

D halo	Reducing agent	Monohalo	% yield	Temp, °C
$Cl_2C(COOC_2H_5)_2$	Na_2SO_3	$ClCH(COOC_2H_5)_2$	82	20
	NaSH		5	−15
$Cl_2C(COOC_2H_5)PO_3(C_2H_5)_2$	Na_2SO_3	$ClCH(COOC_2H_5)PO_3(C_2H_5)_2$	98	20
	SnF_2		<5	0
$Br_2C(COOC_2H_5)_2$	NaSH	$BrCH(COOC_2H_5)_2$	12	−20
	SnF_2		97	0
$Br_2C(COOC_2H_5)PO_3(C_2H_5)_2$	NaSH	$BrCH(COOC_2H_5)PO_3(C_2H_5)_2$	<5	0
	SnF_2		75	0

TABLE IV

PHYSICAL AND ANALYTICAL DATA FOR DIHALOPHOSPHONOACETATES AND DIHALOMALONATES

Compd	Registry no.	Yield,[a] %	C, % Calcd	C, % Found	H, % Calcd	H, % Found	P, % Calcd	P, % Found	Mol wt, % Calcd	Mol wt, % Found	Bp (mm), °C	$n^{25}D$
$Cl_2C(COOC_2H_5)_2$	20165-81-5	59	36.7	36.7	4.4	4.4			229	230	87 (2.4)	1.4404
$Br_2C(COOC_2H_5)_2$	631-22-1	68	26.4	26.9	3.1	2.9			318	310	76–80 (0.3)	1.4830
$Cl_2C(COOC_2H_5)PO_3(C_2H_5)_2$[b]	5823-12-1	80	32.8	32.1	5.1	5.3	10.6	10.8	293	280	115–118 (0.05)	1.4540
$Br_2C(COOC_2H_5)PO_3(C_2H_5)_2$[c]	28845-75-2	79	25.2	24.7	3.9	4.0	8.1	8.1	382	370	125–128 (0.06)	1.4916

[a] Distilled yield. [b] ^{31}P nmr, δ −7.5. [c] ^{31}P nmr, δ −7.0.

TABLE V

PHYSICAL AND ANALYTICAL DATA FOR MONOHALO DERIVATIVES

Compd[b]	Registry no.	Bp (mm), °C	$n^{25}D$	^{31}P nmr,[a] δ (ppm)	C, % Calcd	C, % Found	H, % Calcd	H, % Found	P, % Calcd	P, % Found	Mol wt, % Calcd	Mol wt, % Found
$[(i\text{-}C_3H_7)_2O_3P]_2CHCl$	20107-67-9	105–108 (0.05)	1.4465	−11.5 (d, J = 18.2 Hz)	41.3	41.2	7.7	7.9	16.4	16.5	378.5	365
$[(i\text{-}C_3H_7)_2O_3P]_2CHBr$	10596-20-6	140 (0.03)	1.4528	−11.5 (d, J = 17.5 Hz)	37.0	37.1	6.8	7.5	14.65	14.8	423	400
$[(C_2H_5)_2O_3P]_2CHBr$	28845-79-6	127–128 (0.08)	1.4682	−13.0 (m)	29.4	29.1	5.8	5.7	16.9	16.8	367	355
$(C_2H_5)_2O_3P(C_2H_5OOC)CHCl$	7071-12-7	120–124 (0.1)	1.4448	−12.0 (m)	37.1	36.8	6.2	6.2	12.1	12.2	258.5	255
$(C_2H_5OOC)_2CHCl$	14064-10-9	62 (0.1)			43.2	43.9	5.7	6.0			194.5	195
$(C_2H_5OOC)_2CHBr$	685-87-0	87–88 (0.2)	1.4500		37.8	37.5	4.9	4.9			223	235

[a] Chemical shifts relative to 85% H_3PO_4. [b] ^1H nmr spectra were found to be consistent with the assigned structure.

phosphorus nmr spectra were measured using spinning 9-mm glass tubes with a Varian HR-60 spectrometer operating at 24.3 MHz. Chemical shifts are accurate to ±0.5 ppm. Side-band calibration was used. Varian HA-100 and HR-60 spectrometers were used to obtain the proton spectra. Molecular weights were obtained by vapor pressure osmometry.

Tetraalkyl dihalomethylenediphosphonates were prepared according to the method of Quimby, *et al.*[2] Triethyl dihalophosphonoacetates and diethyl dihalomalonates were also prepared by the hypohalite procedure[2] without significant modification. Table IV reports yields, analyses, and physical characteristics of these materials.

Monohalo derivatives of methylenediphosphonate, phosphonoacetate, and malonate esters were all prepared by the same general procedure. The preparation of tetraisopropyl chloromethylenediphosphonate is considered typical and is given in detail below. Physical characteristics and elemental analyses of the monohalo derivatives prepared by this procedure are collected in Table V. Other information pertinent to their syntheses can be found in Tables I, II, and III.

Tetraisopropyl Chloromethylenediphosphonate.—A solution of sodium hydrosulfide (28 g, 0.5 mol) in 200 cc of water was slowly added to tetraisopropyl dichloromethylenediphosphonate (206.7 g, 0.5 mol) in 200 cc of methanol. The temperature was maintained at 25° throughout the addition. Precipitation of sulfur was noted with the initial addition of NaSH. After addition was complete, the solution was stirred for *ca.* 0.5 hr and then filtered to remove the sulfur (14.8 g, 92.5%). The filtrate was extracted with $CHCl_3$ and the organic portion was dried over Na_2SO_4. Removal of solvent left 185.6 g of a colorless liquid (98%). A ^{31}P nmr spectrum indicated 95% purity. Vacuum distillation gave the pure title compound (see Table V for further details).

Reaction of Sodium Sulfide and Tetraisopropyl Dichloromethylenediphosphonate. Preparation of $[(i\text{-}C_3H_7)_2O_3P]_2CHSSCH[PO_3(i\text{-}C_3H_7)_2]_2$ (I).—Equimolar quantities of Na_2S (39 g, 0.5 mol) and tetraisopropyl dichloromethylenediphosphonate (206.7 g, 0.5 mol) were combined at room temperature in a water–methanol solvent. The resulting mixture was stirred 3 hr at 25° and the temperature was raised to 75° and maintained there for 1 hr. The product was isolated by $CHCl_3$ extraction. After removal of the solvent, the remaining liquid was dissolved in petroleum ether. Compound I crystallized from this solution on cooling. It was recrystallized from hexane–petroleum ether (bp 30–60°) (yield 25–50%, mp 99.5–101.5°): δ −15.2 (d, J = 19 Hz). The ^1H nmr spectrum was consistent with the structure proposed for I.

Anal. Calcd for $C_{26}H_{58}O_{12}P_4S_2$: C, 41.6; H, 7.8; P, 16.5; S, 8.5; mol wt, 750.8. Found: C, 41.5; H, 7.7; P, 16.5; S, 8.8; mol wt, 750.

Registry No.—I, 28845-76-3.

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Developmental Photochemistry. The Norrish Type II Reaction

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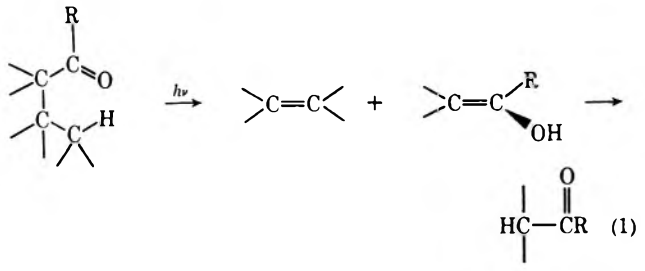
The Norrish type II photochemical reaction results in the splitting of an appropriately substituted ketone into olefinic and enolic fragments (eq 1).[2] The reaction proceeds facilely provided that hydrogens γ to the carbonyl group are available and that the group R (commonly aryl) is devoid of strongly electron withdrawing or donating substituents. The efficacy of this method of carbon–carbon bond cleavage prompted us to devise means of using it as a preparative route to various olefins. Such an effort is practical only if (a) syntheses of starting materials are straightforward involving less work than the preparation of the desired olefinic product by a more classic route, and (b) the olefinic product can be isolated and purified readily. We have found that these conditions can be met uniquely for the preparation of a number of fairly volatile alkenes and dienes.

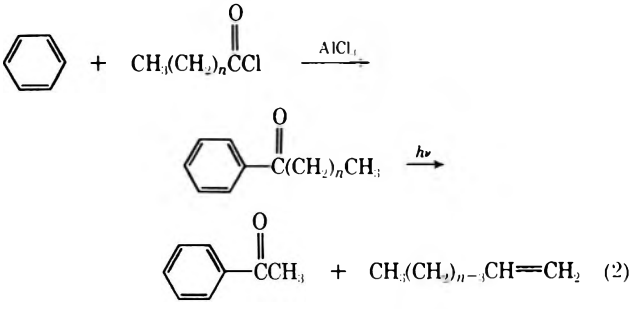


(1)

Results and Discussion

To make the photochemical reaction practical on a synthetic scale, we designed a simple reaction flask attached by means of ground-glass joints to a quartz-jacketed medium-pressure Hanau TQ-81 lamp. A distillation head with condenser was fitted to the flask and the receiver was held in liquid N_2. By means of a manostat any desired vacuum could be maintained in the apparatus which was mounted in a variable temperature bath. The ketone to be irradiated (*ca.* 10 g) was dissolved or suspended in a high-boiling solvent (tetramethylene glycol dimethyl ether). The solution, stirred magnetically, was put under the desired vacuum and warmed to 40–50°. The lamp was then switched on. During irradiation, the alkene fragment, as soon as it formed, was distilled out of solution into the receiving flask cooled in liquid nitrogen. Neither the starting material nor the ketonic fragment (designed to be nonvolatile, *vide infra*) codistils to a serious extent under these conditions. The alkene product may be purified further by normal procedures.

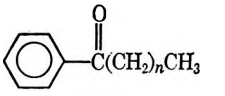
Ketonic precursors to simple linear olefins are obtained easily from the reaction of the appropriate acyl chloride with benzene (eq 2). Irradiation under above



(2)

described conditions leads to olefin which distils smoothly away from starting material and the other photochemical product, acetophenone. As can be seen from Tables I and II, quite satisfactory yields of simple terminal olefins may be realized.

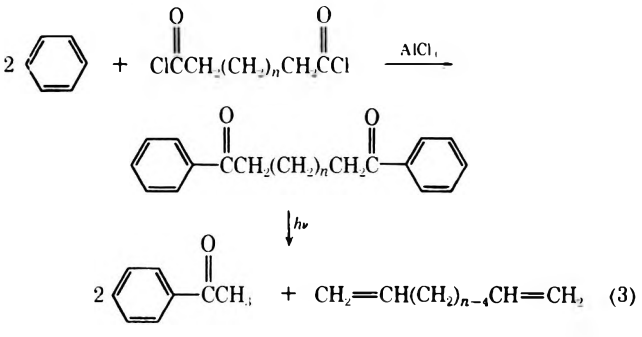
TABLE I
SYNTHESES OF SIMPLE LINEAR OLEFINS



Starting material	Registry no.	Irradiation time, hr	Temp, °C	Product (yield, %)[a]
$n = 6$	1674-37-9	9.5	40	Hexene-1 (74)
$n = 7$	6008-36-2	10	40	Heptene-1 (84)
		48	40	Heptene-1 (78)
$n = 8$	6048-82-4	10	42	Octene-1 (75)
$n = 10$	1674-38-0	10	50	Decene-1 (35)

[a] Based on starting ketone.

Both conjugated and nonconjugated terminal dienes are obtainable by the device of a double elimination on a diketone prepared as shown in eq 3. Again, acceptable



(3)

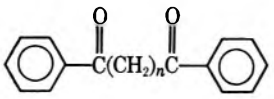
yields are obtained (Table II) except in the attempted synthesis of allene.

Combination of routine synthetic methods and the Norrish type II reaction permits the conversion of a

(1) Fellow of the Alfred P. Sloan Foundation, 1971–1973.

(2) For leading references concerning the structural parameters governing Norrish type II reactions, see (a) D. C. Neckers, "Mechanistic Organic Photochemistry," Reinhold, New York, N. Y., 1967; (b) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965; (c) P. J. Wagner and G. S. Hammond, *Adran. Photochem.*, **5**, 21 (1968).

TABLE II
SYNTHESES OF SOME SIMPLE LINEAR DIENES



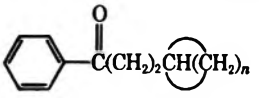
Starting material	Registry no.	Irradiation time, hr	Temp, °C	Product (yield, %)[a]
$n = 6$	6268-58-2	24	40	Butadiene-1,3 (50)
$n = 7$	2886[illegible]-21-4	20	40	Pentadiene-1,4 (46)
		60	40	Pentadiene-1,4 (51)
$n = 8$	6268-61-7	20	30	Hexadiene-1,5 (53)
$n = 5$	2886[illegible]-22-5	20	30	Allene (0)[b]

[a] Based on starting ketone. [b] 1-Phenylpenta-4-en-2-one was the only isolated product.

flask designed was sufficient so that solid ketone slowly went into solution as the photochemical reaction progressed still leading to acceptable yields. This problem was particularly pronounced with several of the diketones.

The chief limitation of the method derives from volatility considerations. Any olefin whose boiling point under reduced pressure approaches that of acetophenone will be contaminated with the latter. Likewise, olefins not appreciably more volatile than the solvent will necessarily codistil with it. An additional problem is that the photochemical reaction itself fails in certain more esoteric cases as illustrated by the unsuccessful synthesis of allene.[4]

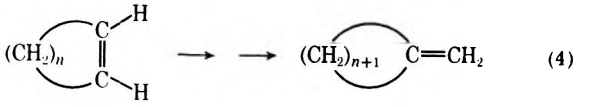
TABLE III
SYNTHESES OF TERMINAL OLEFINS USING NORRISH TYPE II REACTIONS



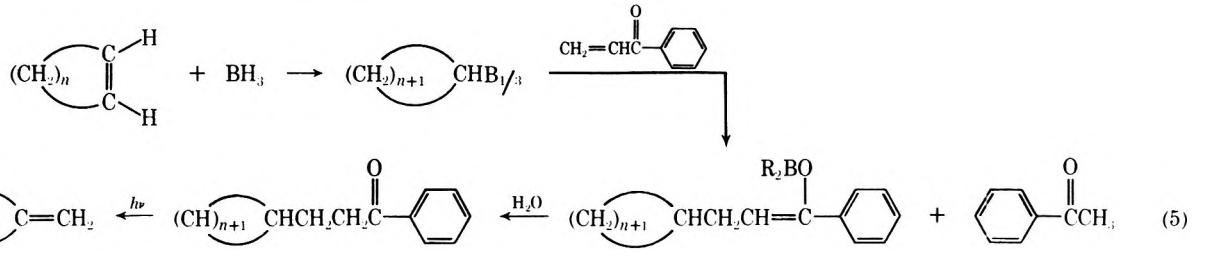
Starting material[a]	Registry no.	Irradiation time, hr	Temp, °C	Product (yield, %)[b]
$n = 7$	28861-23-6	24	40	Methylenecyclooctane (34)
$n = 5$	28861-24-7	24	40	Methylenecyclohexane (54)
$n = 4$	28861-25-8	24	40	Methylenecyclopentane (68)
3-(2-Norbornyl)-1-phenylpropanone	28861-26-9	24	40	2-Methylenenorbornane (30)
3-(3′-Tetrahydropyranyl)-1-phenylpropanone	28861-27-0	24	40	3-Methylenetetrahydropyran (34)

[a] Crude product prepared from alkene as described in the Experimental Section. [b] Based on starting olefin but corrected for loss of two alkene units as borate (eq 5).

readily ayailable cyclic olefin to a homologous exocyclic isomer (eq 4). The requisite ketones for the Norrish type II reaction were obtained as shown in eq 5



(4)



(5)

and were used without any further purification.[3] As seen from Table III, this approach is remarkably successful and, moreover, considerable variation in the cyclic component is possible as witnessed by the successful syntheses of 2-methylenenorbornane and 3-methylenetetrahydropyran.

Several features of the above reactions deserve comment. First, the olefins and dienes obtained are isomerically pure. In the case of 1-octene, for example, no contaminating 2-octene could be detected by glpc. Second, the synthesis of the dienes reported represents a simple entry into compounds of this sort which are often difficult to prepare isomerically pure in other ways. Finally, even though the starting ketone was not always completely soluble in the solvent, the stirring with the

(3) Method of A. Suzuki, A. A. H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogic, and M. W. Rathke, *J. Amer. Chem. Soc.*, **89**, 5708 (1967).

All things considered, however, the Norrish type II reaction can be adopted successfully to the synthesis of volatile olefins on a preparative scale and may, in certain cases, be the method of choice.

Experimental Section

All melting points and boiling points are uncorrected. A Hanau Model TQ-81 medium-pressure mercury arc lamp was used for the irradiations. Nmr spectra were taken in CCl_4 and are reported in δ values downfield from TMS, internal standard.

General Synthesis of Phenyl Ketones.—The procedure of Vogel[5] was followed for the synthesis of all the phenylated ketones.

Phenyl *n*-heptyl ketone: bp 166–168° (14 Torr); mp 22.2–23.2° (lit.[6] mp 22.2–23.2°).

Phenyl *n*-octyl ketone: bp 176–177° (15 Torr) (lit.[7] mp 17°).

Phenyl *n*-nonyl ketone: bp 187° (14 Torr); mp 34–35° (lit.[6] mp 34–35°).

Phenyl *n*-undecyl ketone: mp 41.1–42.1° (lit.[7] mp 41–42).

(4) The Norrish type II reaction does not lend itself readily to the synthesis of some strained systems. See, for a recent illustration, R. B. Gagosian, J. C. Dalton, and N. J. Turro, *ibid.*, **92**, 4752 (1970).

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1,10-Diphenyl-1,10-dioxodecane: mp 93–94° (lit.[8] mp 92–93°).

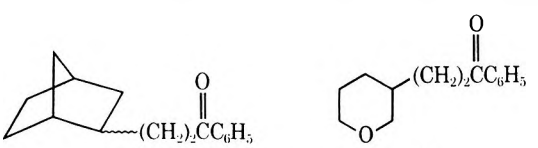
1,9-Diphenyl-1,9-dioxononane: mp 51–53° (lit.[9] mp 55–56°).

1,8-Diphenyl-1,8-dioxooctane: mp 85–87° (lit.[9] mp 91°).

1,7-Diphenyl-1,7-dioxoheptane: mp 65.5–66.5° (lit.[10] mp 65–67°).

Products were identified by comparison of the nmr spectra and ir spectra with those of known samples.

Synthesis of ketonic precursors for terminal olefins was carried out by converting 0.3 mol of the appropriate cycloalkene to the trialkylborane.[3] This borane was partially hydrolyzed with 4.5 g (0.25 mol) of water whereupon 23.7 g (0.18 mol) of phenyl vinyl ketone[11] in 100 ml of THF was added. After 1 hr at 25° the THF was removed and the reaction mixture was held at 60° for 1 hr at 15 mm to remove volatile components. The irradiations were carried out with these crude mixtures. Samples of the respective ketones were isolated as their 2,4-dinitrophenylhydrazones (2,4-DNP): 3-cyclohexyl-1-phenylpropanone-1, mp (2,4-DNP) 179–180°; 3-cyclopentyl-1-phenylpropanone-1, mp (2,4-DNP) 157–159°; 3-cyclooctyl-1-phenylpropanone-1, mp (2,4-DNP) 151–152°; 3-(2-norbornyl)-1-phenylpropanone-1 (a), mp (2,4-DNP) 151–153°; 3-(3′-tetrahydropyranyl)-1-phenylpropanone (b) failed to yield an acceptable derivative; boron hydride is known, however, to add only to the 3 position of 4,5-dihydropyran.[12]



a

b

Methylenecyclohexane,[13] methylenecyclopentane,[13] methylenecyclooctane,[14] and 2-methylenenorbornane[15] had physical properties identical with those of authentic materials. 3-Methylenetetrahydropyran after purification by preparative glpc had n^{20}D 1.4398; nmr (CCl_4) δ 1.70 (multiplet, 2,5 H), 2.28 (t, broadened, 2, J = 6.8 Hz, 4 H), 3.60 (t, 2, J = 5.0 Hz, 6 H), 3.92 (s, 2, 2 H), and 4.68 (s, 2, methylene OH); ir (neat) 3080, 1650, 1070, and 915 cm^{-1}. The mass spectrum had the parent peak at m/e 98.

Acknowledgment.—One of the authors (D. C. N.) thanks the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

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Ozonolysis of Unsaturated Phosphorus Compounds[1]

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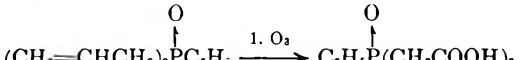
Ozonization has been used only rarely[2] as a synthetic reaction in organophosphorus chemistry except for the oxidation of phosphines to phosphine oxides.[3] Nevertheless, the technique is of general potential use in the high-yield oxidation of olefinic and acetylenic phosphine oxides to the related carboxylic acids.

Oxidation of diallylphenylphosphine oxide by ozone followed by decomposition in the presence of hydrogen peroxide and formic acid gave 2,2′-(phenylphosphinylidene)diacetic acid (**1**) in an 83% yield. Bromination of the methylene positions, formation of the corresponding anhydride, or decarboxylation *via* a Hunsdiecker reaction on **1** did not afford the desired products. The products of these reactions were not fully characterized. Esterification of **1** with methanol in the presence of sulfuric acid, with methanol and thionyl chloride, or with methyl iodide and base failed to yield the desired ester. However, when **1** was allowed to react with diazomethane, dimethyl-2,2′-(phenylphosphinylidene)-diacetic acid (**2**) was obtained. The methylene position of **2** was also unreactive toward bromination.



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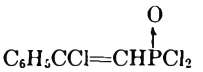
2

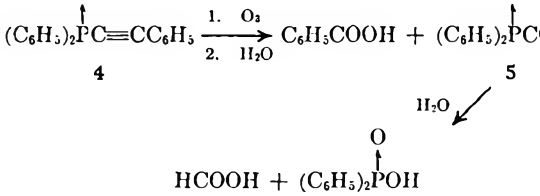
In the course of a related investigation, 2-chloro-2-phenylvinylphosphonic dichloride (**3**) was allowed to



3

react with phenylmagnesium bromide. The product obtained with 3 mol of Grignard reagent was phenylethynyldiphenylphosphine oxide (**4**). Characterization of **4** was based on the absence of a vinylic proton in the nmr spectrum, the distinct presence of the triple bond in the infrared spectrum, a melting point of a mixture of **4** and an authentic sample of **4**, and elemental analysis.

Ozonization of phenylethynyldiphenylphosphine oxide (**4**) gave benzoic acid, formic acid, and diphenylphosphinic acid. It has been shown[4] that the probable



intermediate, diphenylphosphinylideneformic acid (**5**), is unstable under hydrolysis conditions. In a similar manner, ozonization of 1,2,3,4,5-pentaphenylphosphacyclopentadiene oxide with excess ozone caused complete decomposition of the ring structure to give phenylphosphonic acid and 4 equiv of benzoic acid.

(1) This work was supported by a grant, GP-5659, from the National Science Foundation.
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(3) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965, p 166.
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Experimental Section[5]

2,2′-(Phenylphosphinylidene)diacetic Acid (1).—Through a solution of 5.16 g (0.025 mol) of diallylphenylphosphine oxide[6] in 40 ml of methanol was passed ozonized oxygen at −78° until a blue color appeared (about 4 hr). The solvent was evaporated to give a clear, glassy, viscous material which was treated at −78° with 35 ml of 97% formic acid and 17 ml of 30% hydrogen peroxide and was stirred at room temperature overnight. The mixture was then heated to the reflux temperature for 2 hr, the solvents were evaporated, and the residue was triturated with ether to give a total of 5.0 g (83%) of 1: mp 148–151° (lit.[7] 152–154°); nmr (D_2O) δ 7.6 (m, 5), 4.7 (HDO), 3.48 (d, 4, J = 14.5 Hz); ir (KBr) 3000, 1730 (C=O), 1440 (C_6H_5P), 1250 (P→O), 1120, 895, 748, 691, 662 cm^{-1}. *Anal.* Calcd for $C_{10}H_{11}O_5P$: C, 49.59; H, 4.59. Found: C, 49.44; H, 4.45.

The nmr of 1 in strong base (sodium hydroxide–deuterium oxide) showed a singlet in the methylene region. A multiplet of low intensity surrounded the base of this signal. When 1 was heated to 145° for 1.5 hr, bubbling occurred; the nmr spectrum of the resulting material had a doublet at 1.72 (J = 13.5 Hz), characteristic of the P–CH_3 group.

Dimethyl-2,2′-(phenylphosphinylidene)diacetic Acid (2).—To a mixture of 90 ml of 40% potassium hydroxide and 400 ml of ether at 0° was added 53.5 g (0.248 mol) of N-methyl-N-nitrosourea. The resulting yellow ether solution was decanted and the solids were washed five times with ether. To the combined ether fractions at 0° was added 30.0 g (0.1238 mol) of 2,2′-(phenylphosphinylidene)diacetic acid (1) in small portions. Considerable gas evolution occurred during addition. The resulting mixture was stirred for 2 hr at 0° and for 8 hr at room temperature. The white solid was filtered, recrystallized from ether, and dried to give 9.6 g (30%) of 2: mp 102–103° (lit.[7] 102–104.5°); nmr ($CDCl_3$) δ 7.65 (m, 5), 3.67 (s, 6), 3.43 (d, 4, J = 15.4 Hz); ir (KBr) 2950, 1740 (C=O), 1440 (C_6H_5P), 1270 (P→O), 1180, 1105, 913, 738, 690 cm^{-1}. *Anal.* Calcd for $C_{12}H_{15}O_5P$: C, 53.37; H, 5.57. Found: C, 53.38; H, 5.23.

Attempts to esterify 1 with methanol in the presence of sulfuric acid with methyl iodide (on the salt of 1) and by treatment of the acid with thionyl chloride followed by methanol did not yield the desired ester. The products of these reactions were not identified.

Phenylethynyldiphenylphosphine Oxide (4).—A mixture of 47 g (0.184 mol) of 2-chloro-2-phenylvinylphosphonic dichloride (3)[8,9] in 250 ml of dry ether was added to a solution of 0.552 mol of phenylmagnesium bromide in 700 ml of dry ether over a period of 1 hr. The mixture was then hydrolyzed with 10% sulfuric acid, washed with 10% sodium bicarbonate solution, dried, and distilled to give an orange, viscous material, bp 240° (0.1 mm). The distillate was recrystallized from ethanol and ether and washed successively with ether to afford 4: mp 102° (lit.[10] 102°); ir (KBr) 3050, 2170 (C≡C), 1490, 1440 (C_6H_5P), 1195 (P→O), 1120, 998, 848, 756, 724, 704, 690 cm^{-1}. The nmr spectrum showed only aromatic and no vinyl signals. A melting point of a mixture of 4 and an authentic sample of 4[10] was not depressed. *Anal.* Calcd for $C_{20}H_{15}OP$: C, 79.40; H, 4.97. Found: C, 79.34; H, 4.82.

Ozonization of Phenylethynyldiphenylphosphine Oxide (4).—Ozone was bubbled for 6.5 hr through a solution of 5 g (0.016 mol) of 4 in 200 ml of dry carbon tetrachloride at 0°. The resulting blue solution was combined with 150 ml of water and stirred overnight. A white solid precipitated and was filtered and dried to give 3.1 g (90%) of product. The melting point (189–192°) and infrared spectrum matched those of diphenylphosphinic acid.[11] The filtrate was reduced by evaporation to afford more solid. Filtration gave a small amount of material, mp 120–122°; a melting point of material mixed (50:50) with benzoic acid was 120–122°.

Ozonization of 1,2,3,4,5-Pentaphenylphosphacyclopentadiene Oxide.—Ozone was bubbled for 4 hr through a solution of 3 g (0.00624 mol) of 1,2,3,4,5-pentaphenylphosphacyclopentadiene oxide and 200 ml of dry chloroform at 0°. After 1 hr the yellow color had disappeared, but it returned by the end of the reaction. While the solution was still cold, 250 ml of water was added. The mixture was then stirred at room temperature overnight, the layers were separated, and the water layer was washed with chloroform. The organic portions were combined, and the chloroform was removed at reduced pressure. Sublimation of the residue gave >2.8 g (93%) of benzoic acid which was identified by its melting point (122°) and comparative infrared spectroscopy. The water layer was partially evaporated, filtered, and then evaporated to dryness to give 0.756 g (86%) of a solid. An infrared spectrum of this material was identical with that of phenylphosphonic acid.[11]

Registry No.—1, 17166-71-1; 2, 17166-66-4; 4, 7608-18-6; 1,2,3,4,5-pentaphenylphosphacyclopentadiene oxide, 1641-63-0.

(5) Nmr spectra were taken on a Varian A-60 spectrophotometer with tetramethylsilane as an internal standard. Infrared spectra were taken on a Perkin-Elmer Model 21 double beam recording spectrophotometer. Melting points were taken on a Mel-Temp melting point block which was calibrated with known standards. Elemental analyses were performed by the University of Iowa Chemistry Department and by Micro-Tech Laboratories, Inc. Ozone was generated by a Welsbach, Model T-23 ozonator.

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The Synthesis of *N*-Alkylanilines *via* Aryne Reaction in Primary Aliphatic Amine Solvent[1a]

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Dehydrobenzene has so far found its widest area of synthetic application in the addition of ammonia and secondary amines.[2] Surprisingly, no detailed investigation concerning the addition of primary aliphatic, acyclic amines to aryne has been reported. One would expect that this reaction would yield readily isolable *N*-alkylanilines in a convenient one-step synthesis. This note reports the results (Table I) of the addition of various

Table I

Reaction of Bromobenzene and Sodamide in Various Primary Aliphatic Amine Solvents

Solvent, RNH_2, R	I, C_6H_5NHR, yield, %
n-C_3H_7	74
i-C_3H_7	71
n-C_4H_9	78
i-C_4H_9	72
sec-C_4H_9	72
tert-C_4H_9	72

primary aliphatic amines to benzyne generated by the action of sodamide on bromobenzene.

$$C_6H_5Br + NaNH_2 + RNH_2 \longrightarrow \underset{\text{I}}{C_6H_5NHR}$$

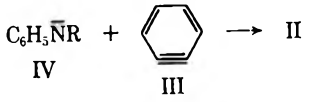
It was found that this reaction is general and that good yields (71–78%) of corresponding *N*-alkylaniline I are obtained using a reaction time of 6 hr at room temperature and a sodamide–bromobenzene mole ratio

(1) (a) Supported in part by Grant N-118 of the Robert A. Welch Foundation, Houston, Texas. (b) To whom correspondence should be addressed. (c) Robert A. Welch Undergraduate Fellow.

(2) For a comprehensive listing, see R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967, p 115.

of 3:1. Production of I in greater yields was precluded by the formation of higher phenylated *N*-alkylanilines II (*ca.* 20–25%).[3]

The formation of I most likely occurs by the addition of the neutral solvent molecule to benzyne (III). Lyate anion addition to III is unlikely because of the relative low acidity of primary aliphatic amines toward sodamide. However, I is converted readily to its conjugate base $C_6H_5\bar{N}R$ (IV) due to phenyl substitution. The increased reactivity of IV as compared to that of the solvent molecules results in the formation of appreciable quantities of II by the addition of IV to III.



This method provides a convenient means of preparing pure *N*-alkylanilines and is the method of choice for preparation when the *N*-alkyl group is sterically hindered or subject to isomerization. For example, *N-tert*-butylaniline (V) (72% in this study) is produced in only a 12% yield *via* alkylation at atmospheric pressure.[4] A higher yield (60%) of V has been obtained in a patented process utilizing high-pressure alkylation techniques.[5] In addition, the yields of *N*-isobutylaniline (72%) and *N-sec*-butylaniline (72%) obtained in this study are vastly superior to those previously reported.[6,7]

Experimental Section

Sodamide was obtained from Fisher Scientific Co. and was used as received. All manipulations of sodamide were carried out in a drybox. Amine solvents, obtained from Eastman Kodak, were dried over anhydrous calcium hydride for 24 hr and then distilled directly into a thoroughly dried reaction flask. Bromobenzene was dried over calcium chloride and distilled before use.

General Procedure.—All reactions were carried out under a nitrogen atmosphere. To a stirred mixture containing 300 ml of amine solvent and 11.7 g (0.3 mol) of sodamide was added 15.7 g (0.1 mol) of bromobenzene. The reaction mixture was then stirred for 6 hr (a color change to orange occurs after 1–3 hr of stirring) and then quenched by the addition of 18.4 g (0.35 mol) of ammonium chloride. The solvent was removed by distillation and collected. The residue was combined with ether and stirred, and the solids were removed by filtration. The product was extracted from the ether layer with 10% HCl. The aqueous extracts were made basic with $NaHCO_3$ and 10% NaOH and extracted with ether. Drying of the ether layer by anhydrous $MgSO_4$ followed by vacuum distillation yielded the desired products.

The physical properties of the products are: *N-n*-propylaniline, bp 119–121° (31 mm) [lit.[8] bp 98.5–100° (11 mm)], $n^{25}D$ 1.5420 (lit.[8] $n^{22}D$ 1.5406); *N*-isopropylaniline, bp 111–113° (36 mm) [lit.[9] bp 198–206° (760 mm)], $n^{25}D$ 1.5355 (lit.[9] $n^{25}D$ 1.5380); *N-n*-butylaniline, bp 105–107° (6.5 mm) [lit.[6a] 124–126° (25 mm)], $n^{25}D$ 1.5331 (lit.[6a] $n^{25}D$ 1.5298); *N*-isobutylaniline, bp 119–120° (25 mm) [lit.[6a] 90° (7 mm)], $n^{27}D$ 1.5281 (lit.[6a] $n^{20}D$ 1.5328); *N-tert*-butylaniline, bp 112–114° (36 mm) [lit.[5] bp 208–211° (760 mm)], $n^{25}D$ 1.5260 (lit.[5] $n^{20}D$ 1.5270); *N-sec*-butylaniline, bp 113–114° (24 mm) [lit.[7] 96–98° (10 mm)], $n^{25}D$ 1.5319 (lit.[7] $n^{20}D$ 1.5333).

Mass spectral, nmr, and ir analyses of all the products were consistent with the proposed structures.

Registry No.—Bromobenzene, 108-86-1; sodamide, 7782-92-5.

(3) Nmr and mass spectral analyses indicate that these higher phenylated products were essentially the corresponding *N*-alkyldiphenylamines together with smaller amounts of the *N*-alkyldiphenylamines.

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2,3-Dihydroquinoxaline 1,4-Dioxides as Intermediates in the Reaction between Benzofurazan 1-Oxide and Enamines

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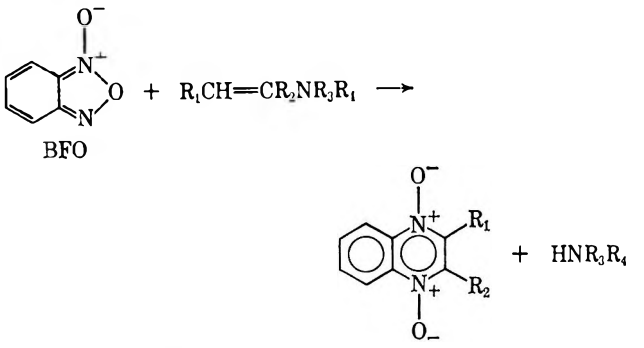
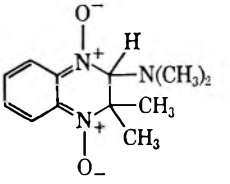
A one-step preparation of quinoxaline 1,4-dioxides from benzofurazan 1-oxide (BFO) and enamines was reported by Haddadin and Issidorides in 1965.[1] Dur-



ing the course of a typical reaction, deep red colors are observed; these eventually disappear during work-up, and the products generally consist of yellow crystals. In an effort to trap an intermediate, BFO was allowed to react with *N,N*-dimethylisobutenylamine,[2] an enamine which cannot undergo a β elimination of dimethylamine. There was obtained from this reaction deep-red crystals of a compound, mp 135–137°. Analysis of the substance and the determination of its nmr, uv, and mass spectra suggested that it was 2-dimethylamino-2,3-dihydro-3,3-dimethylquinoxaline 1,4-dioxide (**1**), a nonaromatic cyclic polyene system.



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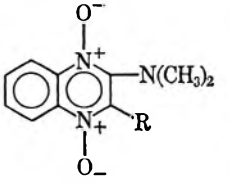

2, R = H
3, R = CH_3

In order to establish the nonaromatic character of **1**, the fully aromatic and closely analogous 2-dimethylaminoquinoxaline 1,4-dioxides **2** and **3** were prepared for comparison. The uv spectrum of **1** has as its longest wavelength absorption maximum a peak at 482 nm. The corresponding maxima for **2** and **3** occur at some

(1) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965).

(2) A gift from Eastman Chemical Products, Inc., Kingsport, Tenn. 37662.

60–70 nm shorter wavelength. In the nmr spectra, protons on the carbocyclic ring of **1** absorbed energy at a higher magnetic field than do the corresponding protons on **2** and **3**. The absorption due to the proton at C-2 on **1** is shifted 4.0 ppm upfield with respect to that of the proton at C-3 on **2**. All these facts speak for the nonaromatic character of **1** and for the assigned structure.

The compound **1** was synthesized under conditions comparable to those reported earlier for the preparation of quinoxaline 1,4-dioxides from BFO.[1] Further, the color of **1** in solution approximates that observed during the course of more typical reactions which lead to fully aromatic compounds. It follows that 2,3-dihydroquinoxaline 1,4-dioxides are likely intermediates in the reaction between BFO and enamines; also, this same possibility cannot be ignored in considering intermediates in the reaction between BFO and carbanions.[3]

Experimental Section

2-Dimethylamino-2,3-dihydro-3,3-dimethylquinoxaline 1,4-Dioxide (1).—A stirred solution of 13.6 g (0.1 mol) of BFO in 100 ml of $CHCl_3$ was treated dropwise over a period of 30 min with a solution of 9.9 g (0.1 mol) of *N,N*-dimethylisobutenylamine[2] in 50 ml of $CHCl_3$. During the addition the temperature rose spontaneously but slowly to 37° and the reaction solution turned deep red. The temperature remained at 37° for 15 min and then dropped slowly to room temperature. The reaction mixture was allowed to stand overnight. The $CHCl_3$ was evaporated under reduced pressure, and the dark-red residue was eluted by C_6H_6–$CHCl_3$ (1:1) on a column of Florisil to afford 12 g of a dark crystalline substance which was recrystallized from Me_2CO–C_6H_{14} to give garnet-colored crystals, yield 4.5 g, mp 119–123°. Two further recrystallizations furnished an analytically pure sample of **1**: yield 3.5 g (15%); mp 135–137°; uv max (H_2O) 251 nm (ϵ 17,200), 482 (9320); nmr (CCl_4) δ 1.49 (s, 3, *trans*-3-CH_3), 1.52 (s, 3, *cis*-3-CH_3), 2.34 (s, 6, NCH_3), 4.20 (s, 1, 2 H), 6.6–6.9 (m, 2), 7.2–7.5 (m, 2); mass spectrum (70 eV) *m/e* (rel intensity) 235 (6), 192 (11), 177 (14), 99 (100), 84 (83).

Anal. Calcd for $C_{12}H_{17}N_3O_2$: C, 61.3; H, 7.3; N, 17.9. Found: C, 61.2; H, 7.1; N, 18.0.

2-Dimethylaminoquinoxaline 1,4-Dioxide (2).—In a reaction vessel equipped with a reflux condenser, a stirred solution of 1.36 g (0.01 mol) of BFO in 50 ml of $CHCl_3$ was treated dropwise over a period of 2 min with 1.14 g (0.01 mol) of *N,N,N',N'*-tetramethyl-1,1-vinylidenediamine.[4] The temperature rose spontaneously to the boiling point of the mixture and after 5 min began to fall. When the reaction mixture was at room temperature a yellow crystalline precipitate formed. The crude product was recrystallized from $CHCl_3$–C_6H_{14} to give 1.1 g (54%) of **2**, mp 177–180°. One further recrystallization afforded the analytical sample: mp 178–180°; uv max (MeOH) 239 nm (sh, ϵ 10,300), 279 (24,800), 305 (sh, 9340), 354 (8500), 422 (6200); nmr ($CDCl_3$) δ 3.20 (s, 6, NCH_3), 7.84 (m, 2), 8.20 (s, 1), 8.40 (m, 2).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.4; N, 20.5. Found: C, 58.3; H, 5.2; N, 20.4.

2-Dimethylamino-3-methylquinoxaline 1,4-dioxide (3) was prepared from *N,N,N',N'*-tetramethyl-1,1-propenylidenediamine[4] in a manner similar to that described above: yield 39%; mp 124–127° (Me_2CO–C_6H_{14}); uv max (H_2O) 240 nm (ϵ 20,000), 276 (16,200), 310 (8500), 341 (sh, 9250), 352 (10,900), 411 (5000); nmr ($CDCl_3$) δ 2.70 (s, 3, CCH_3), 3.06 (s, 6, NCH_3), 7.72 (m, 2), 8.48 (m, 2).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 6.0; N, 19.1. Found: C, 60.3; H, 5.9; N, 19.2.

Registry No.—**1**, 29086-42-8; **2**, 29086-43-9; **3**, 29086-44-0.

(3) (a) C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, **31**, 4067 (1966); (b) K. Ley, F. Seng, U. Eholzer, R. Nast, and R. Schubart, *Angew. Chem., Int. Ed. Engl.*, **8**, 596 (1969).

(4) H. Bredereck, F. Effenberger, and H. P. Beyerlin, *Chem. Ber.*, **97**, 3081 (1964).

Acknowledgment.—The technical assistance of Mr. David A. Johnson was a valuable asset to the completion of this work. Also, I would like to express my appreciation to Professor Hans Muxfeldt for helpful advice.

Preparation of Substituted 1,2-Benzoisothiazolin-3-one 1,1-Dioxides (o-Benzoic Sulfimides)

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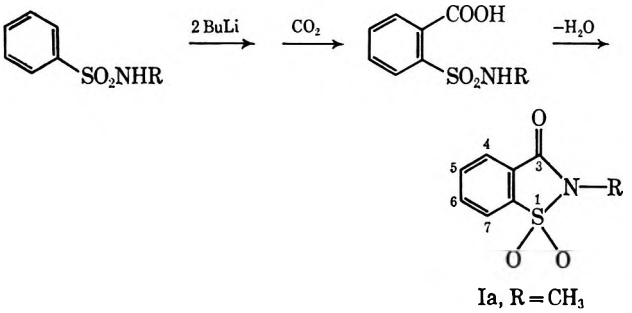
Ortho lithiation of *N*-methyl- and *N*-phenylbenzenesulfonamides followed by carbonation and cyclization has previously been reported[1] to produce *N*-methyl- and *N*-phenyl-1,2-benzoisothiazolin-3-one 1,1-dioxide (Ia,b), in 49 and 22% yields, respectively (Scheme I).

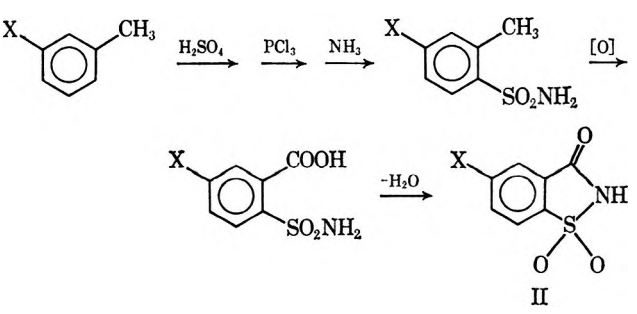
SCHEME I



Ia, R = CH_3
b, R = C_6H_5

In connection with another study, fairly large quantities of certain 5-substituted 2*H*-1,2-benzoisothiazolin-3-one 1,1-dioxides (*i.e.*, 5-substituted *o*-benzoic sulfimides) (II) were required. The multistep preparation of a few such compounds has been reported (Scheme II)

SCHEME II



II

utilizing vigorous oxidation of *o*-toluenesulfonamides. The latter compounds are obtained *via* sulfonation of a substituted toluene, and cyclodehydration of the *o*-sulfamoylbenzoic acid gives II. The reported procedures did not appear promising, however, since

(1) H. Watanabe, R. Gay, and C. R. Hauser, *J. Org. Chem.*, **33**, 900 (1968).

TABLE I

SUBSTITUTED *N-tert*-BUTYLARYLSULFONAMIDES[a]

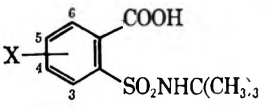
$ArSO_2NHC(CH_3)_3$

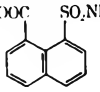
Ar	Registry no.	Yield, %	Mp, °C	Crystn[b] solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	2512-24-5	94	78–80		$C_{10}H_{15}NO_2S$	56.31	7.09	6.57	56.34	7.06	6.73
4-$CH_3C_6H_4$	2849-81-2	97	111–114	E	$C_{11}H_{17}NO_2S$	58.11	7.54	6.16	58.36	7.59	5.90
4-ClC_6H_4	29083-03-2	74	119–121	E	$C_{10}H_{14}ClNO_2S$	48.48	5.69	5.65	48.46	5.69	5.61
4-$CH_3OC_6H_4$	2849-81-2	55	102–104	E	$C_{11}H_{17}NO_3S$	54.29	7.04	5.76	54.05	7.17	5.46
4-FC_6H_4	29083-05-4	97	87–89	I	$C_{10}H_{14}FNO_2S$	51.93	6.10	6.06	51.71	6.18	5.83
2-Naphthyl	24293-49-0	81	146–148	E	$C_{14}H_{17}NO_2S$	63.84	6.51	5.32	63.78	6.62	5.12
1-Naphthyl	29083-07-6	96	149–151	E	$C_{14}H_{17}NO_2S$	63.84	6.51	5.32	63.68	6.33	5.30

[a] Prepared from the corresponding arylsulfonyl chloride and *tert*-butylamine as illustrated in the Experimental Section for *N-tert*-butylbenzenesulfonamide. [b] E = ethanol; I = isopropyl alcohol.

TABLE II

SUBSTITUTED 2-(*N-tert*-BUTYLSULFAMOYL)BENZOIC ACIDS[a]



X	Registry no.	Yield, %	Mp, °C (dec)	Crystn[b] solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	29104-99-2	48	105–107	B–H	$C_{11}H_{15}NO_4S$	51.34	5.88	5.44	51.35	5.96	5.60
5-CH_3	29083-08-7	28	149–151	EA–H	$C_{12}H_{17}NO_4S$	53.11	6.32	5.16	53.27	6.48	4.90
5-Cl	29083-09-8	25[c]	145–147	E	$C_{11}H_{14}ClNO_4S$	45.28	4.84	4.80	45.42	5.00	4.59
5-OCH_3	29083-10-1	27	165–168	E	$C_{12}H_{17}NO_5S$	50.16	5.96	4.87	49.79	6.03	4.76
5-F	29083-11-2	35	143–146	H	$C_{11}H_{14}FNO_4S$	48.10	5.13	5.09	47.88	5.09	5.38
5,6-$(CH)_4$	29083-12-3	30	173–176	B	$C_{15}H_{17}NO_4S$[d]	62.40[d]	5.85	4.05	61.98	5.80	3.93
	29083-13-4	14	214–216	E–H	$C_{15}H_{17}NO_4S$	58.60	5.58	4.56	58.40	5.65	4.52

[a] Prepared from the corresponding *N-tert*-butylarylsulfonamide using *n*-butyllithium and carbon dioxide as illustrated in the Experimental Section for 5-methyl-2-(*N-tert*-butylsulfamoyl)benzoic acid. [b] EA = ethyl acetate; H = hexane; E = ether; B = benzene. [c] Better yields were obtained when the reaction was carried out at −60° and powdered carbon dioxide was added to the dilithio salt. [d] Obtained as a 0.5 benzene solvate after drying at room temperature under vacuum.

yields were either not reported or very low[2–4] or difficulties were encountered with purification of the final products.[5] Other methods for preparing *o*-benzoic sulfimides are equally difficult or require several-step procedures.[6,7]

The method of Hauser[1] for preparing I appeared attractive for preparing compounds of type II *if* an R group could be found which could be easily replaced by a hydrogen atom in the final product. An R group is necessary for the reaction with butyllithium since primary arylsulfonamides (*e.g.*, benzenesulfonamide) failed to metalate in the ortho position.

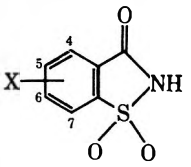
The benzyl group was found to be unsatisfactory as the R group. Preparation of 2-benzyl-5-methyl-1,2-benzoisothiazolin-3-one 1,1-dioxide (**8**) from *N*-benzyl-*p*-toluenesulfonamide proceeded smoothly in two steps (see Experimental Section); however, no conditions could be found for debenzylating **8**. Unsuccessful debenzylation attempts, resulting in the recovery of unchanged **8**, included the use of hydrogen and palladium or platinum in a variety of solvents, as well as hydrobromic acid in acetic acid and aqueous hydrochloric acid in ethanol. Similar failures resulted from repeated attempts to debenzylate the known[8] 2-benzyl-1,2-benzoisothiazolin-3-one 1,1-dioxide.

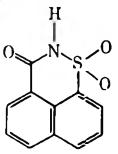
On the other hand, a *tert*-butyl substituent proved to be admirably suited as a protecting group in the preparation of II (Scheme I, R = *tert*-butyl). Ortho lithiation and carbonation of *N-tert*-butylarylsulfonamides (Table I) produced the desired substituted 2-(*N-tert*-butylsulfamoyl)benzoic acids (Table II). The latter compounds were smoothly cyclized *and* dealkylated in one step by polyphosphoric acid to give the desired substituted 1,2-benzoisothiazolin-3-one 1,1-dioxides, **1**–**5** (Table III). Application of the same reaction sequence to 2- and 1-(*N-tert*-butyl)naphthalenesulfonamides gave products carbonated at the 1 and 8 positions, respectively, which in turn produced the previously known **6** (1,2-dehydro-1-oxonaphth[1,2-*d*]-isothiazole 3,3-dioxide) and **7** (2,3-dihydro-3-oxonaphtho[1,8-*de*]-1,2-thiazine 1,1-dioxide) (Table III), respectively. Functional groups sensitive to *n*-butyllithium could not be employed. Thus, when 4-bromo-*N*-(*tert*-butyl)benzenesulfonamide was used in this method, complete debromination occurred to give *o*-benzoic sulfimide ("saccharin") as the final product in high yield. 4-Chloro-*N*-(*tert*-butyl)benzenesulfon-

(2) W. Noyes, *Amer. Chem. J.*, **8**, 167 (1886).
(3) R. DeRoode, *ibid.*, **13**, 217 (1891).
(4) G. Hamor and B. Reavlin, *J. Pharm. Sci.*, **56**, 135 (1967).
(5) C. Whitehead, J. Traverso, J. Bell, and P. Willard, *J. Med. Chem.*, **10**, 844 (1967).
(6) R. Ponci, T. Vitali, F. Mossini, and L. Amoretti, *Farmaco, Ed. Sci.*, **22**, 991 (1967).
(7) E. Muller Ed., "Methoden der Organischen Chemie," Georg Thieme Verlag, Stuttgart, 1955, p 626.
(8) H. Eckenroth and G. Koerppen, *Chem. Ber.*, **29**, 1048 (1896).

TABLE III

SUBSTITUTED 1,2-BENZOISOTHIAZOLIN-3-ONE 1,1-DIOXIDES[a]



No.	X	Yield, %	Mp, °C	Crystn[b] solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	H[c]	51	225–227[c]	E							
2	5-CH_3	57	203–205		$C_8H_7NO_3S$	48.72	3.58	7.10	48.73	3.65	6.95
3	5-Cl	34	212–215		$C_7H_4ClNO_3S$	38.63	1.84	6.44	38.69	1.91	6.21
4	5-OCH_3	53	237–239[d]	E	$C_8H_7NO_4S$	45.04	3.31	6.57	45.05	3.44	6.45
5	5-F	23	218–220	Et	$C_7H_4FNO_3S$	41.79	2.00	6.96	41.82	2.02	6.85
6	4,5-$(CH)_4$	39	244–247[e]	I	$C_{11}H_7NO_3S$	56.64	3.03	6.01	56.40	2.97	5.92
7		62	267–269[e]	I	$C_{11}H_7NO_3S$	56.64	3.03	6.01	56.45	3.04	5.94

[a] Prepared from the corresponding substituted 2-(*N-tert*-butylsulfamoyl)benzoic acid and polyphosphoric acid as illustrated in the Experimental Section for compound **2**. [b] E = ethanol, Et = ether, I = isopropyl alcohol; where no solvent is indicated, product was obtained analytically pure from the reaction. [c] "Saccharin," lit. mp 225–228°, mmp 225–227°. [d] R. D. Haworth and A. Lapworth, *J. Chem. Soc.*, **125**, 1306 (1924), report mp 242°. [e] H. Kaufmann and H. Zobel, *Chem. Ber.*, **55B**, 1499 (1922), report mp 244° for 6 and mp 265° for compound **7**.

amide gave improved yields of ortho-carbonated product when the reaction was carried out at −60°. Except for these restrictions, the method appears to be a versatile, superior technique, even on fairly large scale, for converting arylsulfonyl chlorides to substituted 1,2-benzoisothiazolin-3-one 1,1-dioxides.

Experimental Section[9]

Arylsulfonyl chlorides were purchased from either Eastman Chemical Co. or Aldrich Chemical Co. and used as received. *n*-Butyllithium in hexane was purchased from Foote Chemical Co.

***N-tert*-Butylbenzenesulfonamide.**—To a stirred solution of 32.9 g (0.45 mol) of *tert*-butylamine in 75 ml of dry chloroform at 0° was slowly added a solution of 26.5 g (0.15 mol) of benzenesulfonyl chloride in 100 ml of chloroform. The cooling bath was removed and the suspension was stirred 1 hr at room temperature. After 1 hr at reflux, the suspension was cooled and washed successively with 200-ml portions of 3 *N* hydrochloric acid and then water (twice). The chloroform layer was dried (Na_2SO_4) and evaporated to give 30 g (94%) of analytically pure product, mp 77–80°. See Table I.

5-Methyl-2-(*N-tert*-butylsulfamoyl)benzoic Acid.—To 13.6 g (0.060 mol) of *N-tert*-butyl-*p*-toluenesulfonamide in 400 ml of dry tetrahydrofuran at 0° in a thoroughly dried three-necked round-bottom flask was added 120 ml (0.18 mol) of 1.6 *M* *n*-butyllithium in hexane. After 10 min at 0° the reaction was stirred for 1–2 hr at room temperature (samples of the reaction were carbonated, and thin layer chromatography on Eastman chromagram sheets, Type 6060, using benzene–5% acetic acid as eluent was employed to follow the course of these reactions). Carbon dioxide was then bubbled through the reaction for 0.5 hr[10] followed by the addition of 200 ml of water and 40 ml of 12 *N* HCl. After evaporation (reduced pressure, minimum heat applied) to one-half volume, chloroform extracts of the residual mixture were dried over $CaSO_4$. Evaporation of solvent and recrystallization (see Table II) gave the product, mp 149–151° dec.

5-Methyl-1,2-benzoisothiazolin-3-one 1,1-Dioxide (2).—A yellow suspension of 0.50 g (0.019 mol) of 5-methyl-2-(*N-tert*-butylsulfamoyl)benzoic acid in 20 ml of polyphosphoric acid was heated (steam bath) for 15 min while mixing manually with a spatula. The thick syrup was poured (hot) in a thin stream onto an excess of crushed ice which was vigorously stirred. Filtration of the solid and a thorough wash with water gave 0.21 g (57%) of analytically pure product: mp 203–205° (see Table III); nmr (DMSO-d_6) τ 7.49 (s, 3, CH_3), 3.33 (broad, 1, NH, exchanges in D_2O), 2.2–1.8 (m, 3, aromatic protons).

2-Benzyl-5-methyl-1,2-benzoisothiazolin-3-one 1,1-Dioxide (8).—This compound was prepared from *N*-benzyl-*p*-toluenesulfonamide [mp 113–115° (lit.[11] mp 115–116°)] by the lithiation–carbonation procedure described above. The resultant semicrystalline material, after infrared spectral comparison to authentic 2-(*N*-benzylsulfamoyl)-5-methylbenzoic acid (9) (see below), was found to be suitable for use in the next step.

A solution of the above semisolid in 500 ml of benzene containing 50 mg of *p*-toluenesulfonic acid was refluxed for 3 hr. After evaporation of all solvent and recrystallization from ethanol, there was obtained 3.7 g (37%) of **8**: mp 133–135°; nmr (DMSO-d_6) τ 7.48 (s, 3, CH_3), 5.07 (s, 2, CH_2), 1.7–2.7 (m, 8, aromatic protons).

Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88. Found: C, 62.77; H, 4.71; N, 4.85.

2-(*N*-Benzylsulfamoyl)-5-methylbenzoic Acid (9).—A suspension of compound **8** in concentrated ammonium hydroxide was heated in a steel pressure vessel at 125° for 2 hr. After cooling to 0°, careful acidification (hydrochloric acid) gave a quantitative yield of **9**, mp 154–157°. An infrared spectrum was virtually identical with that of the semisolid obtained above from the action of butyllithium–carbon dioxide on *N*-benzyl-*p*-toluenesulfonamide.

Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.0; H, 4.95; N, 4.60. Found: C, 58.58; H, 5.00; N, 4.80.

Registry No.—**1**, 81-07-2; **2**, 29083-15-5; **3**, 29083-16-7; **4**, 29083-17-8; **5**, 29083-18-9; **6**, 29083-19-0; **7**, 29083-20-3; **8**, 29083-21-4; **9**, 29083-22-5.

Acknowledgment.—The author is grateful to Messrs. Harold Ramus, Paul Kelbaugh, and Nelson Treadway, Jr., for their assistance in the synthetic work and to Dr. R. V. Kasubick for determining conditions for large-scale preparations.

(9) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian Associates A-30 spectrometer with tetramethylsilane as an internal standard. Yields reported are for single experiments: no attempts were made to maximize yields in any particular reaction.

(10) A faster method involved pouring the reaction onto a suspension of solid carbon dioxide in ether.

(11) S. Wawzonek and D. Meyer, *J. Amer. Chem. Soc.*, **76**, 2918 (1954).

Bridgehead Nitrogen Heterocycles. V. Some 3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyridines Derived from 2-Trichloromethylthioaminopyridine

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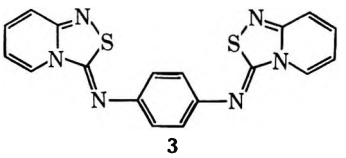
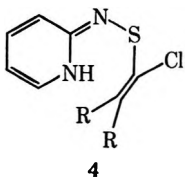
Received November 30, 1970

In a previous communication[2] it was shown that 2-aminopyridines underwent ready reaction with perchloromethyl mercaptan to give 3-(2-pyridylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridines. The reaction involved 2-trichloromethylthioaminopyridine (**1**) as an intermediate and, under carefully controlled reaction conditions, **1** was isolated in a pure and relatively stable state.[3] This present communication deals with the use of this trichloro compound in the synthesis of 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridines with a variety of substituents in the 3 position.

Condensation of 2-trichloromethylthioaminopyridine (**1**) occurred readily with aromatic primary amines (Table I). The products derived from the corresponding aliphatic amines were unstable, but it was possible to characterize that derived from ammonia by conversion into the *p*-nitrobenzoyl derivative. 2,5-Dichloroaniline (pK_a = 1.5) gave the corresponding 3-(2′,5′-dichlorophenylimino)-3*H*-[1,2,4]thiadiazolo-[4,3-*a*]pyridine (**2**, X = 2,5-$Cl_2C_6H_3N$=) in good yield, whereas 2,6-dichloroaniline did not form the fused system. It is possible that ring closure was prevented by steric hindrance between the 3 substituent and the 5-hydrogen atom but, as other products with comparable steric requirements were prepared, a more likely explanation lies in the low basicity of 2,6-dichloroaniline preventing the formation of the intermediate imidoyl chloride. An aromatic diamine such as *p*-phenylenediamine underwent condensation with two molecules of **1** to form bis(3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyrid-3-ylidene)-*p*-phenylenediamine (**3**).



3



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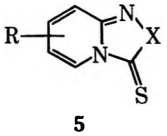

5

Sodium sulfhydrate underwent ready reaction with **1** to yield 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine-3-thione (**2**, X = S). These thiones reacted with methyl iodide to form unstable red salts which could not be characterized. The exocyclic sulfur compounds were stable to acid hydrolysis, as was the corresponding *N*-phenylimino compound **2** (X = NPh).

Suitable enolate anions such as those derived from acetylacetone, acetoacetic ester, diethyl malonate, and ethyl cyanoacetate, also underwent ready condensation with **1** to the fused system **2**. This reaction probably involved displacement of a chloride ion from **1**, followed by elimination of HCl from this product, and subsequent ring closure of the α,β-unsaturated system **4** through a Michael-type addition of the pyridine system. These products, described in Table I, provided strong evidence for the assigned structure of the ring system.

The nmr spectra of the products in Table I were simpler than those of this ring system described earlier[2] and provided confirmation of the earlier assignments. The 3-thione **2** (X = S) and its 5-methyl derivative **2** (X = S; R = 5-CH_3) were particularly informative. The possibility of a Dimroth-type rearrangement[4] occurring in ring systems of this type cannot be overlooked and the alternative structure **5** must be considered. In the case of the 3-thiones **2** (X = S; R = H and 5-CH_3) equivalent structures are produced on rearrangement, whereas with 5-methyl-3-(3′,4′-dichlorophenylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine (**2**, X = 3,4-$Cl_2C_6H_3N$; R = 5-CH_3) rearrangement would result in 2-(3,4-dichlorophenyl)-2,3-dihydro-5-methyl-*s*-triazolo[4,3-*a*]pyridine-3-thione (**5**, X = 3,4-$Cl_2C_6H_3N$; R = 5-CH_3). If this were the case, the 5-methyl group would be under the strong deshielding influence of the 3-thione group and its chemical shift would be equivalent in both compounds. The nmr data[5] for **2** (X = S; R = 5-CH_3) [τ 6.75 (d, 3, $J_{5,6}$ = 1.2 Hz, 5 CH_3), 3.71 (m, 1, $J_{5,6}$ = 1.2 Hz, $J_{6,7}$ = 5.2 Hz, 6 H), 2.76 (m, 1, $J_{6,7}$ = 5.2 Hz, $J_{7,8}$ = 6.0 Hz, 7 H), 2.85 (m, 1, $J_{7,8}$ = 6.0 Hz, 8 H)] and that for **2** (X = 3,4-$Cl_2C_6H_3N$; R = 5-CH_3) [τ 7.10 (d, 3, $J_{5,6}$ = 1.2 Hz, 5 CH_3), 3.95 (m, 1, $J_{5,6}$ = 1.2 Hz, $J_{6,7}$ = 6.0 Hz, 6 H)] clearly show that in the former the 5-CH_3 group is in a different deshielding environment than in the latter.

Other spectral data provided confirmation of these structures, in particular the extended conjugation evident in the ultraviolet spectra (Table I) and the carbonyl absorption of those compounds derived from **2** and enolate ions. Thus, in 3-(diacetylmethylidene)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine (**6**) the carbonyl absorption occurred at 1660 cm^{-1}, indicative of an α,β-unsaturated ketone. Such an absorption is incompatible with the corresponding isomeric structure **5**. Similar absorptions were observed with the other compounds of this type.

An interesting feature of the nmr spectrum of 3-(diacetylmethylidene)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine was the appearance of the methyl resonance as an extremely sharp, ringing-out singlet at τ 7.50. This could not be split into two peaks at −28° or by the addition of pyridine. This symmetry may be explained

(1) (a) Partial support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged. (b) National Dairy Fellow, 1969–1970.

(2) K. T. Potts and R. Armbruster, *J. Org. Chem.*, **35**, 1965 (1970).

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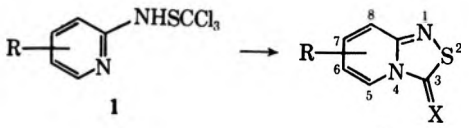
(4) For a recent review, see M. Wahren, *Z. Chem.*, **7**, 241 (1969).

(5) The nmr spectra of the two 3-thiones were calculated from the observed chemical shifts and coupling constants using a LAOCN-3 program (A. A. Bothner-by and S. Castellano, Program 111, Quantum Chemistry Program Exchange, Indiana University, 1968). The chemical shifts and peak intensities of the calculated spectra were in close agreement with the experimental spectra.

TABLE I

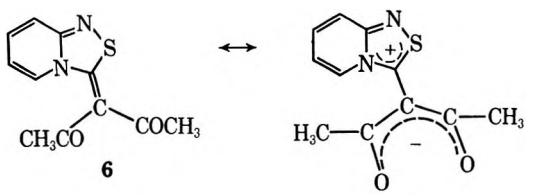
SOME DERIVATIVES OF THE 3*H*-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINE SYSTEM



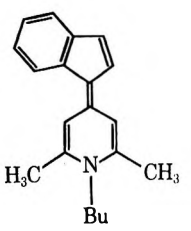
R	Substituents, 3 position	Registry no.	Mp, °C	Color	Crystal habit	Recrystn solvent[a]	Method of preparation[b]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$\nu_{C=N}$ (KBr), cm^{-1}	$\lambda_{max}^{CH_3OH}$ nm (log ϵ)
H	N-C_6H_5	28912-70-1	104–105	Yellow green	Plates	E	IB	60	$C_{12}H_9N_3S$	63.41	3.99	18.49	63.47	4.10	18.77	1630	390 (3.83), 295 (4.20), 238 (4.30), 220 (4.25)
H	N-*p*-$CH_3C_6H_4$	28912-71-2	108–109	Yellow	Rhombs	E	IB	65	$C_{13}H_{11}N_3S$	64.70	4.61	17.41	64.92	4.53	17.34	1625	395 (3.96), 295 (4.35), 242 (4.42)
H	N-(2,5-$Cl_2C_6H_3$)	28912-72-3	123–124	Yellow	Needles	E	IA	50	$C_{12}H_7Cl_2N_3S$	48.66	2.38	14.19	48.76	2.49	14.15	1620	385 (4.04), 300 (4.25), 240 (4.50)
5-CH_3	N-(3,4-$Cl_2C_6H_3$)	28912-73-4	149–150	Pale green	Needles	E	IA	70	$C_{13}H_9Cl_2N_3S$	50.36	2.93	13.55	50.53	2.88	13.68	1640	400[c] (4.15), 385 (4.19), 313 (4.44), 242 (4.72)
			248[d]	Green	Needles	F	ID	40	$C_{18}H_{12}N_6S_2 \cdot {}^1/_4CH_3COOH$	56.76	3.28	21.72	56.78	3.28	21.72	1610	410 (4.25), 325 (4.47), 240 (4.52)
H	N-(1-$C_{10}H_7$)	28912-74-5	121	Green	Irregular prisms	G	IB	35	$C_{16}H_{11}N_3S$	69.29	4.00	15.15	68.95	3.90	14.62	1610	400 (3.18), 328 (3.72), 240 (4.15)
H	N-($CH_2C_6H_5$)	28912-75-6	80–82	Yellow	Needles	G	IC	50	$C_{13}H_{11}N_3S$	64.70	4.60	17.41	64.15	4.56	17.85	1640	395[c] (3.58), 380 (3.62), 285 (3.78), 240 (4.30)
H	N-(*p*-$NO_2C_6H_4CO$)	28912-76-7	>300	Lime green	Irregular prisms	H	II	15	$C_{19}H_9N_4SO_3$	51.99	2.68	18.66	51.54	2.61	18.58	1640	370 (4.68), 265 (4.65)
H	S	28912-77-8	145–147	Golden brown	Plates	G	III	35	$C_6H_4N_2S_2$	42.83	2.40	16.65	42.72	2.36	16.56	1625	388 (3.83), 322 (3.72), 368 (3.72), 265 (3.50), 235 (4.07)
5-CH_3	S	28912-78-9	112–113	Yellow	Needles	G	III	45	$C_7H_6N_2S_2$	46.13	3.31	15.37	45.92	3.12	14.98	1645	395 (3.83), 340 (3.68), 328 (3.65), 240 (2.99)
H	$C(COCH_3)_2$	28912-79-0	146	Yellow	Irregular prisms	I	IV	30	$C_{11}H_{10}N_2O_2S$	56.39	4.30	11.96	56.14	4.20	11.86	1630	403 (4.29), 330 (4.00), 285 (3.92), 240 (4.27)
H	$C(COCH_3)COOEt$	28912-80-3	140	Yellow	Irregular prisms	I	IV	50	$C_{12}H_{12}N_2O_3S$	54.53	4.58	10.60	54.53	4.57	10.58	1640	395 (4.00), 333 (3.85), 255[c] (3.80), 242 (4.02)
H	$C(COOEt)_2$	28912-81-4	124	Yellow	Irregular prisms	I	IV	40	$C_{13}H_{14}N_2O_4S$	53.09	4.79	9.52	52.97	4.74	9.27	1635	400 (3.95), 330 (4.02), 320 (4.05), 242 (4.34)
H	C(CN)COOEt	28912-82-5	187–189	Pale yellow	Irregular prisms	I	IV	10	$C_{11}H_9N_3O_2S$	53.43	3.67	16.99	53.23	3.67	17.23	1645	410 (3.83), 393 (4.01), 378 (3.95), 328 (3.98), 318 (3.97), 240 (4.10)
7-Br	N-(2-C_6H_4N)	28912-83-6	204–205	Bright yellow	Needles	E	V	60	$C_{11}H_7N_4SBr \cdot {}^1/_2H_2O$	41.78	2.55	17.22	41.75	2.20	17.57	1630	345 (4.22), 328 (4.15), 275 (3.99), 250 (4.22)
7-I	N-(5-I,2-C_6H_4N)	28966-92-9	229–230	Greenish gold	Needles	E	IC	50	$C_{11}H_6I_2N_4S$	27.46	1.47	11.65	27.37	1.23	11.41	1625	385 (4.04), 350 (4.30), 340 (4.21), 288 (4.14)

[a] E = acetone; F = acetic acid; G = ethanol; H = DMF; I = sublimation at 80° (0.5 mm). [b] See Experimental Section. [c] Shoulder. [d] Bis(3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyrid-3-ylidene)-*p*-phenylenediamine.

in terms of a significant amount of single bond character in the exocyclic double bond, resulting in rotation of the exocyclic moiety as shown in **7**. A similar aver-



6 **7**



8

aging effect has been observed[6] for the methyl groups in 1-butyl-1,4-dihydro-2,6-dimethyl-4-inden-1-ylidenepyridine (**8**) where the methyl resonance was a sharp singlet until −20°.

In the mass spectrometer the compounds described above all underwent fission of the 2,3 and 3,4 bonds of the nucleus and gave a 2-thionitrosopyridinium ion which lost NS· forming the pyridyne ion. However, the 3-methylidene derivatives underwent fragmentation of the exocyclic substituents prior to fragmentation of the fused-ring system.

Experimental Section[7]

Synthesis of 2-Trichloromethylthioaminopyridines.—The 2-aminopyridine (0.5 mol) in water (200 ml) was added dropwise with rapid stirring to a water (1000 ml)–ice (500 g) mixture of Cl_3CSCl (0.5 mol), K_2CO_3 (0.5 mol), and 1 g of Alconox. The product precipitated rapidly and was filtered cold in a sintered glass funnel and air-dried. The yield was 70%, with further purification being unnecessary and the stability of the product depending on its dryness and storage in the cold.

(6) G. V. Boyd, A. W. Ellis, and M. D. Harns, *J. Chem. Soc. C*, 800 (1970); see also H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).

(7) All evaporations were done under reduced pressure using a rotatory evaporator. Spectral characterizations were performed with the following instrumentation: ir and uv spectra, Perkin-Elmer Model 337 and Cary Model 14 spectrometer; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer. Melting points were taken in capillaries and microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn., and Instranal Laboratory, Inc., Rensselaer, N. Y.

I. Reaction of 2-Trichloromethylthioaminopyridines with Primary Amines.—The following variety of procedures result in reproducible yields of the products reported in Table I.

A.—The 2-trichloromethylthioaminopyridine (0.02 mol), the amine (0.02 mol), and a large excess of K_2CO_3 (anhydrous) were refluxed in ethanol (300 ml) for 24 hr. After the insoluble material was filtered off, the solvent was removed yielding an oil which crystallized from the appropriate solvent listed in Table I.

B.—The above reactants were stirred at room temperature for 24 hr and the reaction mixture was worked up as in A.

C.—The 2-trichloromethylthioaminopyridine (0.02 mol) and the amine (0.02 mol) were stirred in ethanol (200 ml) at 0° in the presence in Et_3N (0.06 mol) for 2 hr. The solvent was removed and water (50 ml) was added. The resultant oil was extracted with ether and the product finally crystallized from ethanol.

D.—The reaction mixture obtained as in A above was added to water (300 ml) and the residue filtered and recrystallized from glacial acetic acid.

II. Preparation of 3-(*p*-Nitrobenzimido)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine (9).—A stream of ammonia was passed into a chloroform (300 ml) solution of 2-trichloromethylthioaminopyridine (0.05 mol) at 0°. After 2 hr, the NH_4Cl was filtered off and the solvent removed to yield a yellow oil which was dissolved in acetone and *p*-nitrobenzoyl chloride, and K_2CO_3 (anhydrous) was added. After 24 hr at room temperature the precipitate was filtered, washed with water, and then recrystallized from DMF.

III. Preparation of 3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyridine-3-thiones.—The appropriate 2-trichloromethylthioaminopyridine (0.02 mol) was dissolved in ethanol (200 ml) and a solution of NaSH (0.02 mol) was added dropwise with stirring at 0°. After 1 hr the solution was allowed to come to room temperature and, after an additional 3 hr, the solution was filtered and the solvent removed. The resultant oil crystallized from methanol and the product was further purified by sublimation at 100° (bath temperature) (0.03 mm).

IV. Reaction of 2-Trichloromethylthioaminopyridine with Carbanions.—A solution of the active methylene compound (0.02 mol) and KOH (0.02 mol) in ethanol (100 ml) was added dropwise at room temperature to the 2-trichloromethylthioaminopyridine (0.02 mol) in ethanol (400 ml) in the presence of excess K_2CO_3 (anhydrous). After 24 hr the solution was filtered and the solvent removed to yield a dark residue which was dissolved in benzene and passed over an alumina column (1 × 6 in). The effluent solution was evaporated to yield a yellow solid which was sublimed at 130° (bath temperature) (0.03 mm).

V. *In Situ* Generation of 5-Bromo-2-trichloromethylthioaminopyridine and Its Reaction with 2-Aminopyridine.—A solution of 2-amino-5-bromopyridine (0.02 mol) and triethylamine (0.02 mol) in chloroform (50 ml) was added dropwise to a solution of Cl_3CSCl (0.02 mol) in chloroform (300 ml) at 0°. After the addition was completed a solution of 2-aminopyridine (0.02 mol) and triethylamine (0.06 mol) in chloroform (100 ml) was added dropwise and the solution was warmed to room temperature. After 3 hr the solvent was removed and the residue washed with MeOH to yield a yellow solid which was purified by preparative tlc.

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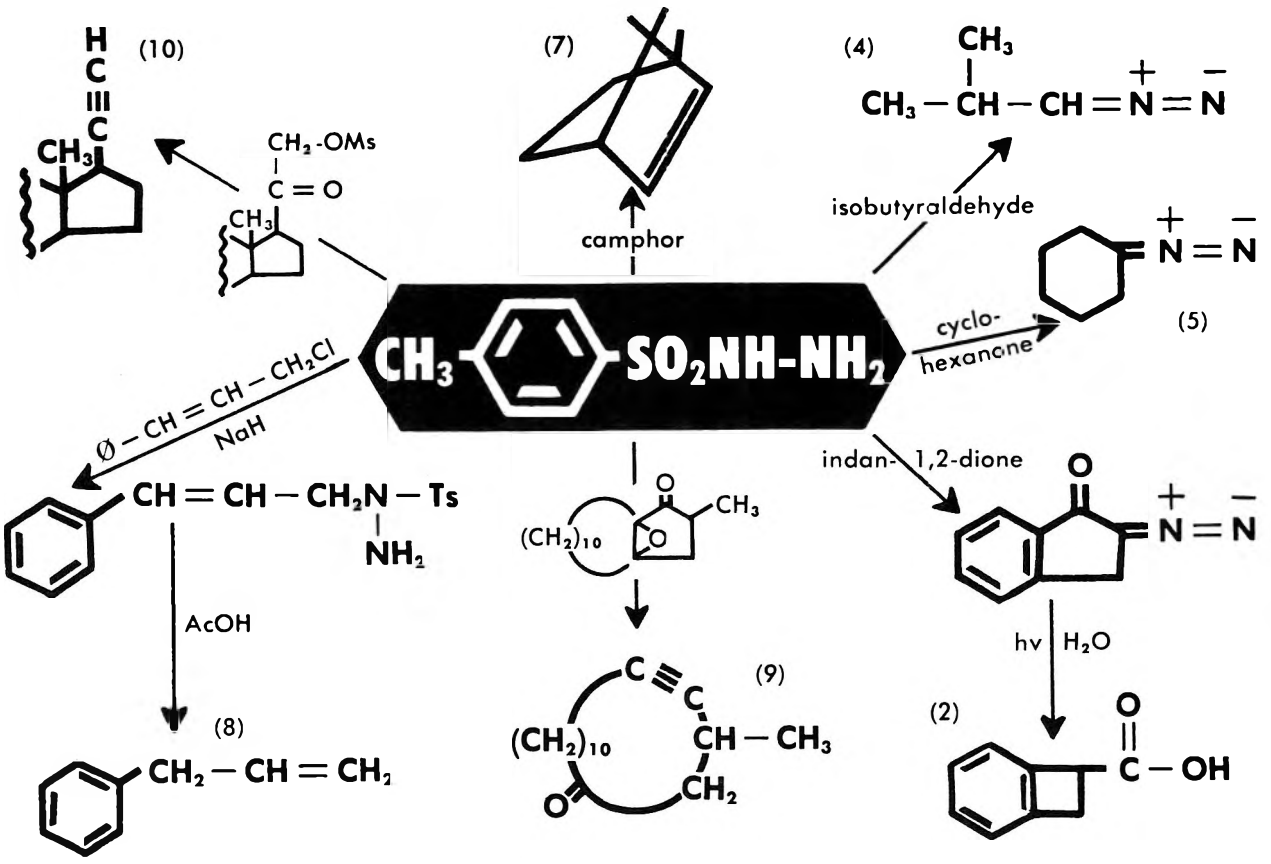

p-Toluenesulfonylhydrazide

A major use of p-toluenesulfonylhydrazide is in the generation of diazo compounds which can then be decomposed *via* carbenes in aprotic solvents or undergo decomposition *via* cationic processes in protic media. An example of the latter is the Bamford-Stevens reaction[1] for converting carbonyl compounds to olefins. α-Diazo ketones are readily generated from α-diketones[2] and can be used synthetically[3] for the preparation of ketenes, α,β-unsaturated ketones, α-aminoketones, α-alkoxyketones, etc. Aliphatic[4] and alicyclic[5] diazo compounds can be considered as homologues of diazomethane and can react with aldehydes and ketones to produce homologous carbonyl compounds and/or epoxides, with carboxylic acids to yield esters and with enols and phenols to give ethers.[6]

Shapiro and Heath[7] introduced a simplified procedure for generating olefins from carbonyl compounds bearing an *alpha* hydrogen. The corresponding p-toluenesulfonylhydrazones were treated with butyl lithium in excess of two equivalents. Allyl halides react with the sodium salt of *p*-toluenesulfonylhydrazice to yield 1-allyl-*p*-toluenesulfonylhydrazides. T. Sato et al[8] have found that warming these compounds in acetic acid causes the double bond to migrate toward the carbon which carries the tosylhydrazide group with elimination of the tosylhydrazide and regeneration of the double bond. This reaction is very clean with no other isomeric olefins being formed. Double bonds even move out of conjugation as in the case of cinnamyl chloride.

In an unusual fragmentation reaction, Eschenmoser et al[9] have utilized p-toluenesulfonylhydrazide to synthesize a large ring ketone from a bicyclic α,β-unsaturated ketone *via* its epoxide. A new synthesis of acetylenes was reported by Wieland[10] who treated 3-β-acetoxy-20-oxo-21-methylsulfonyloxy-5-pregnene with p-toluenesulfonylhydrazide to give 3-oxo-4-pregnene-20-yne.

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See also L. F. Fieser and M. Fieser, **Reagents for Organic Synthesis**, p. 1185 (Wiley) for additional applications and references.

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