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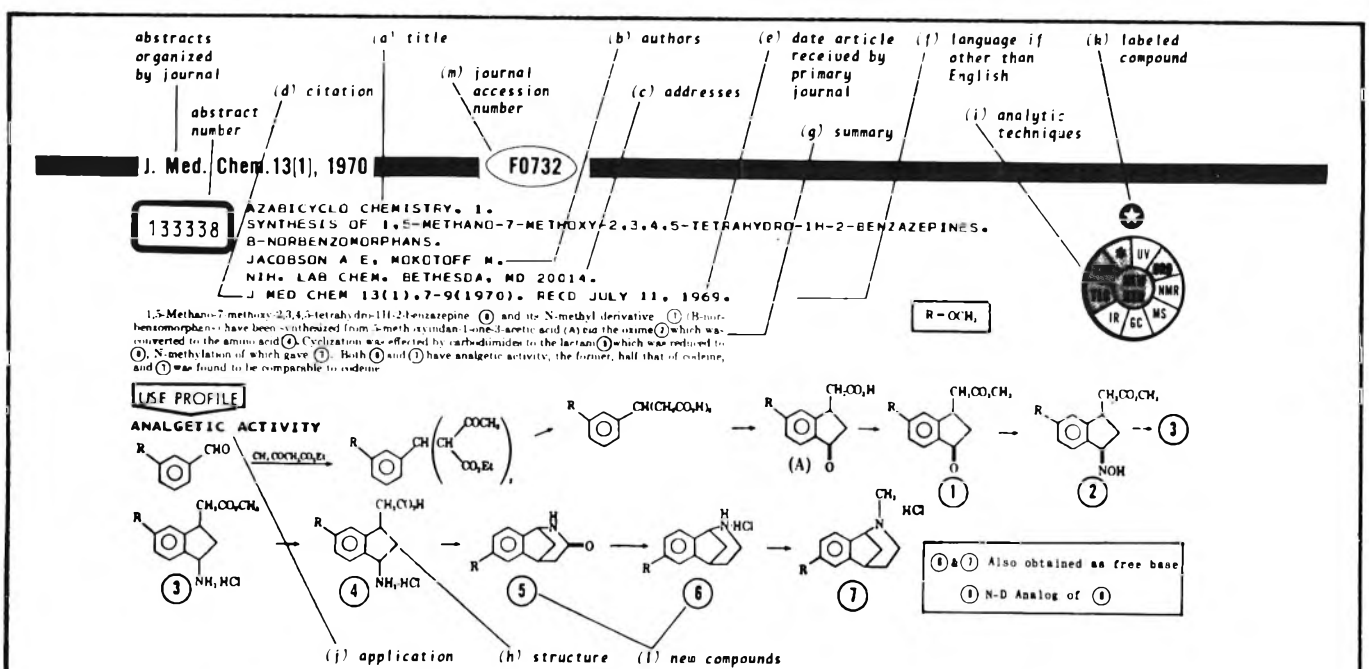

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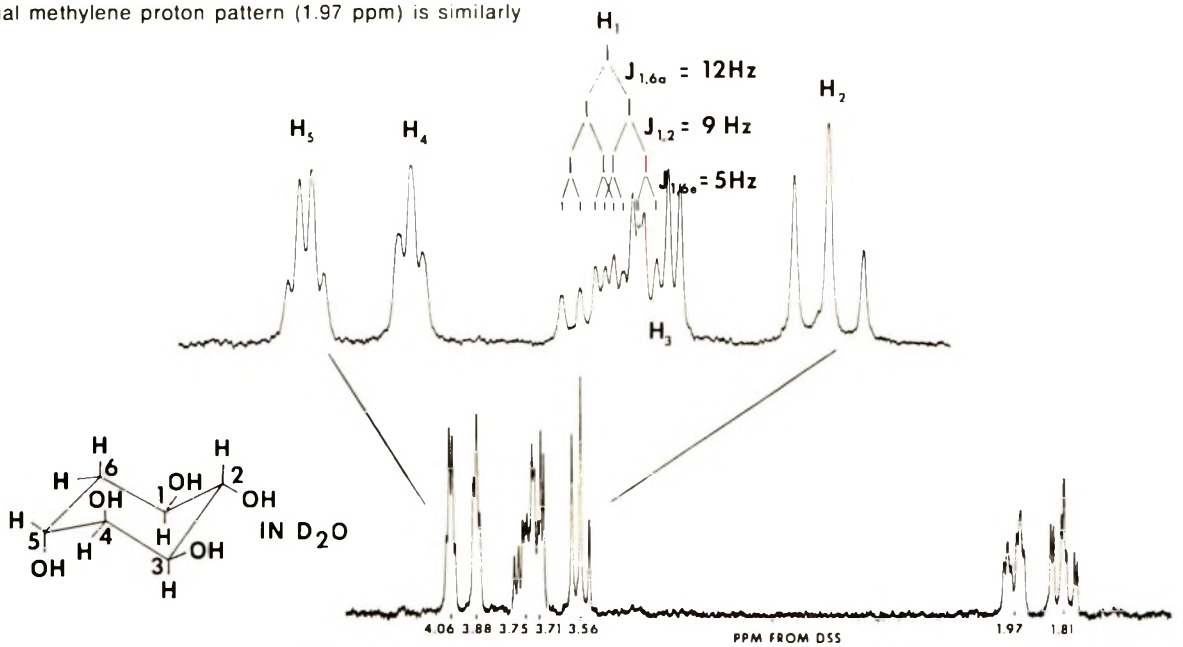
*G. E. McCasland, M. O. Naumann, and L. J. Durham, J. Org. Chem. 33, 4220 (1968). See this reference for corresponding NMR spectra at 60, 100 and 220 MHz.



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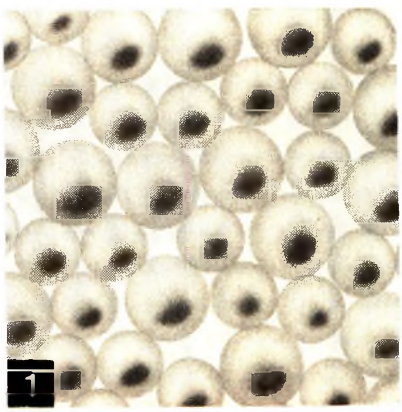

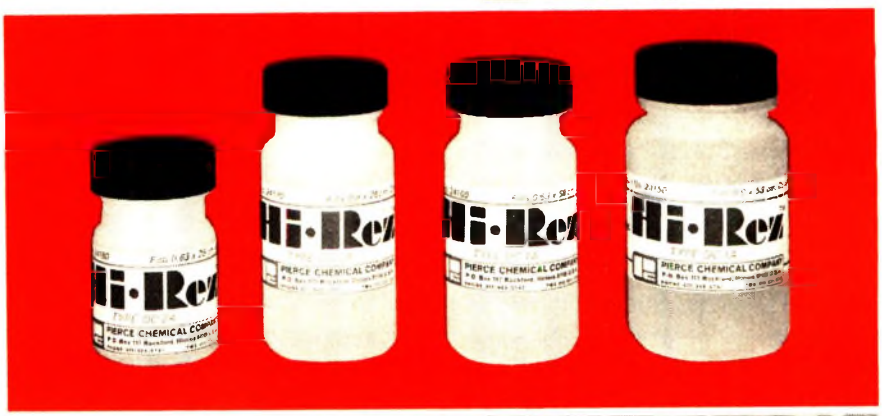

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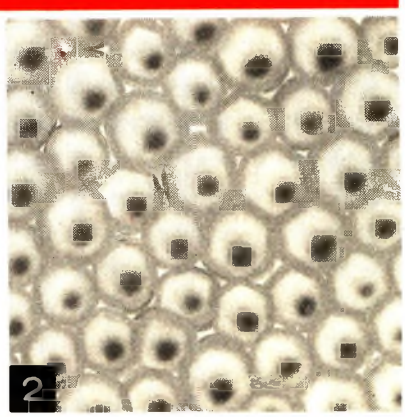

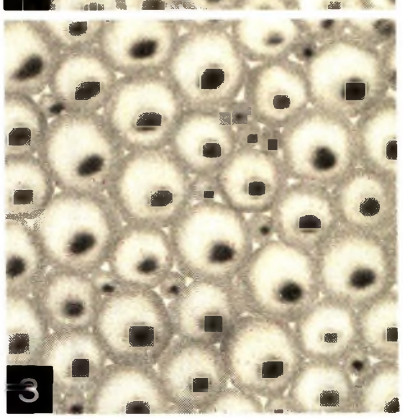

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AUTHOR INDEX

M. S. KHARASCH

Thirty-four years have elapsed since the appearance of the first volume of *The Journal of Organic Chemistry*. The person who, more than anyone else, was responsible for its founding is Morris Selig Kharasch. This issue of the journal, marking the 75th anniversary of his birth, is dedicated to his memory.

A full biographical account of Kharasch and his scientific contributions appears in "Vistas in Free Radical Chemistry," W. A. Waters, Editor, Pergamon Press, 1959. This presentation will attempt to develop such information as is available regarding the start of this journal and the prominent role played by Kharasch. To set the stage, however, it will be helpful to record a few details about Kharasch's life.

He was born on August 24, 1895, at Kremenetz in the Ukraine. At an early age he came with his parents to Chicago where he obtained his schooling. He graduated from Crane High School, Chicago, in 1913, earned a B. S. degree from The University of Chicago in 1917, and a Ph.D. degree in 1919. He served from 1919 to 1922 as a National Research Fellow, then joined the staff of the University of Maryland (Associate Professor, 1922–1924; Professor, 1924–1928). He returned to Chicago as Associate Professor (1928–1930), then Professor (1930–1936), Carl William Eisendrath Professor (1936–1953), and Gustavus F. and Ann. M. Swift Distinguished Service Professor (1953–1957). He was elected to the National Academy of Science in 1948.

Morris Kharasch married Ethel May Nelson in 1923. Their son Robert is a lawyer, and their daughter Elizabeth married Dr. A. David Pearson, a chemist at the Bell Laboratories in New Jersey. A nephew, Norman Kharasch, is Professor of Chemistry at University of Southern California. Morris died in Copenhagen, Denmark, on October 9, 1957.

Following the year 1913 when the *American Chemical Journal* ceased publication as such, American organic chemists had access to but one periodical in this country for their publications, namely, the *Journal of the American Chemical Society*. This fact prompted Kharasch to consider the desirability of another outlet, and it is evident that he discussed the matter with colleagues shortly after his appointment at Chicago in 1928. Those who were parties to such discussions included R. R. Legault, James K. Senior, Otto Reinmuth, and Warren C. Johnson, but no doubt there were many others. Evidently the more he thought about it the more he became convinced that something should be done to inaugurate a publication for papers in organic chemistry. Accordingly, in the early part of 1935 he secured the backing of the Department of Chemistry of The University of Chicago to send a two-page mimeographed letter to a large group of chemists, inquiring into their feelings concerning such a journal if one were started. The letter disclosed that "the Department of Chemistry of The University of Chicago has recently received the offer of limited financial support for the initiation of a new publication in the field of organic chemical research." It mentioned also that Dr. Otto Reinmuth, an associate of Dr. Kharasch and Editor of the *Journal of Chemical Education*, would be "willing to undertake the literary and mechanical editing of the publication."

This was followed by a second letter, signed by Dr. Kharasch and dated August 28, 1935, pointing out the generally favorable reception to the first letter and inviting a group of 34 chemists to serve as members of the Board of Editors. It stated that the names on this list were "selected after careful consideration, in consultation with members of the Executive Committee of the Organic Division and other chemists active in organic research, and are approved by the Executive Committee." Twenty-seven persons of this group accepted and they constituted the first Board of Editors. These names follow.

G. Bryant Bachman, The Ohio State University
Werner E. Bachmann, The University of Michigan
F. W. Bergstrom, Stanford University
Marston T. Bogert, Columbia University
Gerald E. K. Branch, The University of California (Berkeley)
W. S. Calcott, E. I. du Pont de Nemours and Company
Leonard H. Cretcher, Mellon Institute
Nathan L. Drake, University of Maryland
Vincent DuVigneaud, The George Washington University
Henry Gilman, Iowa State College
H. L. Haller, U. S. Department of Agriculture
Arthur J. Hill, Yale University
Charles D. Hurd, Northwestern University
Walter A. Jacobs, The Rockefeller Institute for Medical Research
John R. Johnson, Cornell University
M. S. Kharasch, The University of Chicago
Charles A. Kraus, Brown University
C. S. Marvel, University of Illinois
Thomas Midgley, Jr., Ethyl Gasoline Corporation
J. A. Nieuwland, Notre Dame University
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F. O. Rice, The Johns Hopkins University
H. A. Shonle, The Eli Lilly Research Laboratories
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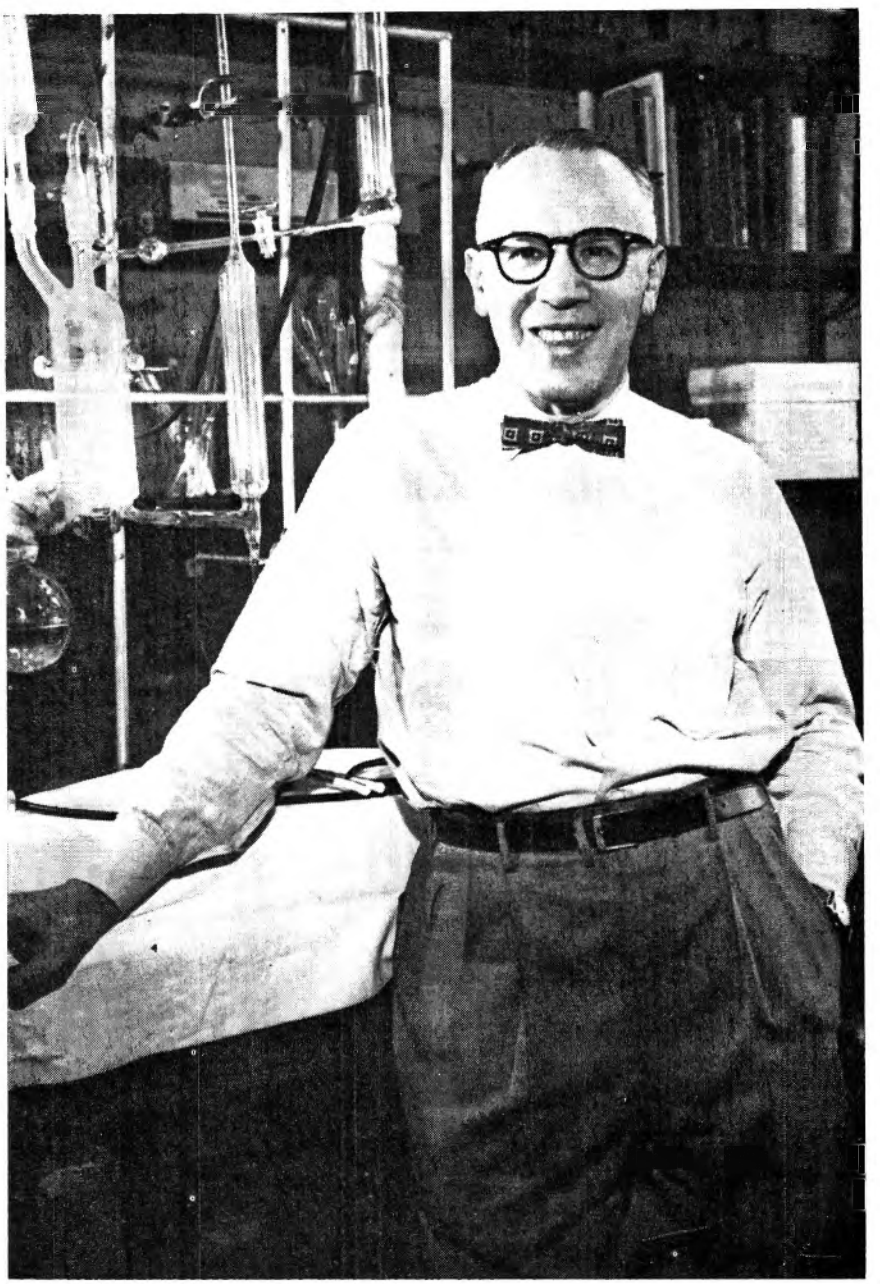

This Board of Editors then sent a report, written essentially by Kharasch, to the membership of the Division of Organic Chemistry of The American Chemical Society. Excerpts of this report follow.

"The original circular letter of the Department of Chemistry of The University of Chicago, outlining a proposal for the establishment of a journal of organic research elicited a response which was 84% favorable.

"These preliminary survey figures were discussed with representatives of The Williams and Wilkins Company, who regarded them as indicating the fiscal feasibility of the project and expressed willingness to undertake publication and guarantee continuation for a period of five years. Publication estimates were based upon six bimonthly numbers of one hundred pages each, in approximately the same format as that of *Chemical Reviews*, at an annual subscription price of six dollars. When necessary, numbers of pages and frequency of issue may be increased either out of excess income or by subsidy. The funds at present pledged are sufficient to cover editorial expense.

"In the belief that such a journal should be conducted under the auspices of the American Chemical Society, the Department of Chemistry of The University of Chicago laid the facts already recounted before President Adams of the Society and Secretary Shriner of the Division of Organic Chemistry. With the encouragement of their interest and approval the Department then extended to the Division, through the Executive Committee, an invitation to sponsor the proposed journal.

"At its New York meeting the Executive Committee unanimously voted to recommend to members of the Division that the Division sponsor the proposed JOURNAL OF ORGANIC CHEMISTRY under the conditions:

(1) that there shall be no financial liability to the Division;
(2) that the policy of the journal shall be determined by a Policy Committee composed of five members.

"In the letter ballot of the members of the Division of Organic Chemistry conducted by the Executive Committee the returns were 92.3% favorable to Division sponsorship.

"A publication contract embodying the terms outlined in the second paragraph of this report has now been executed by The Williams and Wilkins Company (Publisher) and The University of Chicago (fiscal representative of the JOURNAL OF ORGANIC CHEMISTRY).

"Some of the comments, suggestions and qualifications of approval submitted in answer to the original circular letter indicate the desirability of amplifying the former outline of proposed editorial policy.

"While we believe that occasional articles based primarily on theoretical considerations rather than on original experimental work have a proper place in the literature, we do not believe that the JOURNAL OF ORGANIC CHEMISTRY should welcome "reviews" of the pure compilation type. Acceptable reviews should be both critical and interpretative.

"Furthermore, it should be the particular concern of the proposed journal to encourage and to report the type of research which aims at the establishment of new generalizations, or the critical examination and modification, or extension, of old ones.

"When an article necessarily describes a partial contribution to the solution of an extensive problem, some indication of the place of the work in the broader scheme of research should be given. Occasionally when a very extensive piece of work has been published piecemeal over a period of years, a summarizing and correlating article may be in order.

"At all times experimental work should be reported in sufficient detail to make possible its duplication. On the other hand, contributors should not be encouraged to write diffusely or to indulge in purely speculative flights of the imagination.

"It will be the responsibility of the Board of Editors, in cooperation with the Policy Committee, to maintain the editorial policy outlined here and in the previous circular letter and to referee manuscripts submitted for publication—if necessary, with the aid of advice from specialists in various fields.

"Sincerely yours,
The Board of Editors"

From the above it is clear that although the journal was sponsored by the Division of Organic Chemistry of the American Chemical Society it was in no sense owned by the division. Also, it definitely was not an official ACS publication. As to ownership, a letter to the Board of Editors in March 1949 by Editor in Chief Lyndon F. Small mentions "When the Journal was established, the Waverly Press (of Williams and Wilkins) contracted to publish 600 pages (per year), loss if any to be borne by the Press, profits to be divided equally between the Press and The University of Chicago. There has to our knowledge never been any deficit."

Thus, toward the end of 1935, Williams and Wilkins agreed to publish the journal, bimonthly at the outset. Volume 1, no. 1, an issue of 133 pages, appeared in March 1936.

The first meeting of the Board of Editors of the new journal was held in April 1936 at Hotel Muehlebach during the spring meeting of the ACS at Kansas

City, Mo. Eleven board members attended. They elected two members of the five-man Policy Committee, namely, Henry Gilman and J. R. Johnson. The contract with The University of Chicago gave the university the right to appoint one member, namely, M. S. Kharasch. The other two members came from the Organic Division, one (M. T. Bogert) elected by its Executive Committee and the other (R. L. Shriner) being the Secretary of the Division, *ex officio*. Otto Reinmuth served as managing editor until January 1940. The journal served without an editor in chief until 1938 when Small became editor, a position that he held through 1951. In 1952, George H. Coleman replaced Small as editor and he served through 1961. Frederick Greene assumed the editorship in 1962.

The small profits that went to the university were designated for the use and benefit of the journal. The original contract lasted until January 1, 1940, when the university withdrew. A new contract was drawn up, essentially the same as the previous one but with three Editor-Trustees replacing the university. The three so named were Bogert, Gilman, and Small. Again, the contract stipulated that half of any profits would go to the publishers and half to the Editor-Trustees for use in improving and expanding the journal. Except for purchase of a $100 typewriter, voted by the Trustees to replace the battered family machine that Small had been using as editor, not a penny ever went to a member of the editorial board during these years. Professor Gilman adds "When Small was editor, I know how much of the secretarial work that Mrs. Small was doing gratuitously." This type of arrangement continued until 1954 when the American Chemical Society acquired ownership of the journal.

It was the policy of the American Chemical Society in 1935 when the journal started, and vigorously defended by its Executive Secretary Charles L. Parsons, to have a single publication outlet. Dr. Kharasch's desire, however, in the words of Warren Johnson, was "to see the new *Journal of Organic Chemistry* as a separate journal with its own identity." This explains one reason for selection of Williams and Wilkins as publishers. Another reason was that Williams and Wilkins, in a depression year and at considerable financial risk, did agree to the undertaking.

The early years of *The Journal of Organic Chemistry* were scientifically rewarding but certainly not financially rewarding to the publishers. These were the times when several members of the Board approached friends in industry for funds with which to pay for more pages. Organic chemists are very much indebted to Williams and Wilkins Company for its part in keeping the publication alive during these years. They published and printed the first 19 volumes. In January 1955, in a period of relative prosperity, the American Chemical Society became the publisher although Waverly Press continued to print the issues. Volume 21 (1956) was entirely under ACS auspices where it has since remained.

A final point remains. Who was it that made the offer of "limited financial support" to the Chemistry Department of The University of Chicago toward the initiation of this journal? It is amazing how elusive has been the answer to this question. One thinks of such possibilities as The Chemical Foundation or Research Corporation or Williams and Wilkins Company, but executives of these organizations have assured the writer that they possess no record of any such assistance to Dr. Kharasch or The University of Chicago. One thinks of such industries as Du Pont or Lilly with whom Dr. Kharasch was then affiliated as consultant, but an approach to H. W. Elley or H. A. Lubs (of Du Pont) or E. C. Kleiderer (of Lilly), persons who were close to Kharasch in these industries, emphasized the point that they knew of no industrial assistance toward the founding of the journal. One thinks of The University of Chicago but here again the records reveal nothing. W. C. Johnson, vice president of the university, was particularly helpful in searching university records of the Office of the Comptroller and the Minutes of the Board of Trustees from 1934 to 1937. There was no such gift of record made in this period either to the Chemistry Department or to the university.

Another possibility remains, namely, that Kharasch himself sponsored the offer to help. When approached about this possibility, Mrs. M. S. Kharasch could offer no information but she did mention that it would be like him not to tell her if he had done it. Likewise, none of his colleagues that were approached could shed light on the question. The nearest to a disclosure about the source of funds is found in a letter from Kharasch to Small (then Editor in Chief) dated September 26, 1939, and circulated to all members of the Board of Editors. This portion is quoted from the letter:

> "As you doubtless guessed, the subvention granted to the Journal by the University and used to pay the expenses of Dr. Reinmuth (managing editor) does not come out of general university funds. It is derived from outside sources and forms part of an annual donation obtained largely through my own efforts. I have, therefore, a certain obligation both to the University and to the donors to see that this money is well and wisely spent."

So the matter rests. Possibly some benefactor, as yet unrecognized, was the person involved, or possibly it was Dr. Kharasch himself. One thing is certain, however. Whether his contribution to the founding of the journal includes a financial push or not, his initiative in the conception and his drive in getting it successfully started mark him unquestionably as the founder of *The Journal of Organic Chemistry*.

CHARLES D. HURD

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Northwestern University
Evanston, Illinois

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VOLUME 35, NUMBER 8

AUGUST 1970

Diazirines. II.[1] Synthesis And Properties of Small Functionalized Diazirine Molecules. Some Observations on The Reaction of a Diaziridine with the Iodine–Iodide Ion System

R. F. R. CHURCH AND M. J. WEISS

Process and Preparations Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

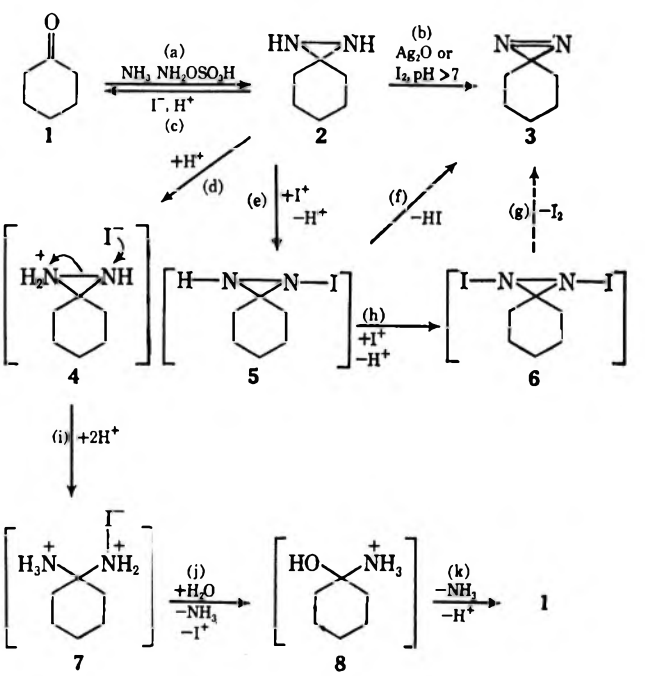
Received December 3, 1969

The use of iodine in triethylamine is presented as a superior alternative to the commonly used silver oxide procedure for the oxidation of diaziridines to diazirines. However, in acidic media this oxidation is not stoichiometric. A study of the iodine–iodide ion redox system with 1,1-hydrazicyclohexane disclosed that a catalytic cyclic process is operative and leads to disproportionation of the diaziridine. Conversely, overconsumption of iodine under conditions of rapid titration is also possible, perhaps owing to the formation of an N,N′-diiododiaziridine intermediate. A variety of simple diazirine-containing aliphatic acids, acid chlorides, esters, alcohols, acetals, aldehydes, amines, amides, etc., were prepared either from the corresponding ketone or by subsequent transformations. The diazirine group was stable to a variety of reagents. The physical properties (pK_a, uv, ir, nmr) of some of these functionalized diazirine-containing molecules are discussed. The effect of the diazirine function on pK_a is approximately comparable with that exerted by a keto group or a chlorine atom, but it is less diminished by increasing distance.

Considerable interest has been generated by the diazirine and diaziridine groups since their unequivocal discovery about ten years ago.[2] In continuation of our study concerning the effect of the diazirine group on biological activity,[1] we have found it necessary to prepare a variety of small, otherwise functionalized molecules which contain this group. In addition to the preparation of some of these compounds, we report herein our observations concerning the compatibility of the diazirine group with a number of common chemical reagents and certain interactions between the diazirine group and neighboring functions. A subsequent report[3] will describe some of the biological properties of these and derived compounds.

The diazirine group is generally introduced by oxidation of the diaziridine obtained from the corresponding ketone by treatment with ammonia and hydroxylamine-O-sulfonic acid or chloramine (Scheme I). Usually, the oxidation (reaction b) is effected by silver oxide which, however, is not an entirely satisfactory reagent for this purpose. Certain functional groups, amines in particular, interfere with the reagent. Furthermore, preprepared silver oxide which is sufficiently active is rather difficult to obtain and, when prepared *in situ* (addition of sodium hydroxide to a solution of silver nitrate and the diaziridine in water or aqueous methanol), several competing side reactions are possible. This oxidation is often sluggish and, since water appears to be the most appropriate solvent, the recovery of

SCHEME I



(1) Diazirines. I: R. F. R. Church, A. S. Kende, and M. J. Weiss, *J. Amer. Chem. Soc.*, **87**, 2665 (1965).

(2) (a) H. J. Abendroth and G. Henrich, *Angew. Chem.*, **71**, 283 (1959); (b) S. R. Paulsen and G. Huck, *Chem. Ber.*, **94**, 869 (1961); (c) E. Schmitz and R. Ohme, *ibid.*, **94**, 2166 (1961).

(3) R. F. R. Church, H. J. Albers, D. Blickens, W. P. Cekleniak, R. Maleike, S. Riggi, and M. J. Weiss, unpublished work.

water-soluble products is troublesome. Probably the most pressing argument against the use of silver oxide is the potential explosive character of the silver mirror formed on the reaction vessel as the oxidation proceeds.[4]

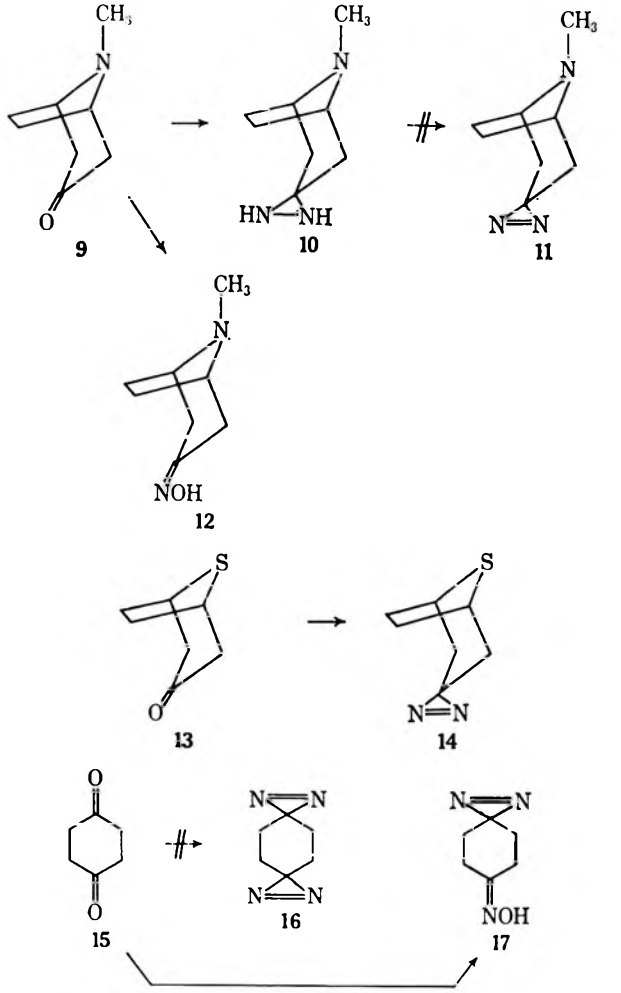
There is a report describing the use of bromine in basic media for this oxidation,[5] and we have found iodine to be at least as useful. This reaction (b in Scheme I, pH >9), which is quantitative and nearly instantaneous, can be carried out by the addition of solid iodine to a methanolic solution of the diaziridine which contains at least one equivalent of triethylamine. After the red color of iodine has persisted for a few seconds, the oxidation is completed by titration with a saturated methanolic solution of iodine (about 0.4 *M*). An important advantage of this method is the apparent absence of side reactions. The method can be used not only in the presence of virtually all functional groups, but the intermediate diaziridine need not be purified or even isolated from the methanolic reaction medium in which it is formed. The only precaution necessary is the complete removal of ammonia prior to adding iodine in order to avoid formation of nitrogen triiodide.[6]

In contrast to this reaction, in which iodine in alkaline media oxidizes the diaziridine function, is the reaction in which iodide ion in acidic media reduces this group.[2a] The latter reaction (c in Scheme I) is typical of diaziridines and is the basis for the standard qualitative test for the group.

We carried out a brief investigation of these reactions with 1,1-hydrazicyclohexane[7] (2) as model substrate. When 2 was titrated with iodine the oxidation reaction b (to the diazirine 3) was rapid and stoichiometric at pH values above *ca.* 9. On the other hand, the reaction was not stoichiometric at pH 7 or below, the amount of iodine consumed being dependent upon the rate of iodine addition. If titrated rapidly (within 1.5 min) at pH 5.0, the consumption of iodine exceeded (up to 15%) the stoichiometric requirement. When the titration was carried out slowly, less than stoichiometric quantities of iodine were consumed. In fact, in acidic media, catalytic quantities (0.05–0.1 mol equiv) of iodine *or* iodide ion caused complete disappearance of the diaziridine if the reaction mixture was allowed to stand sufficiently long (*e.g.*, *ca.* 30 min, pH 5.0, 24°).

These results can be rationalized as follows. In basic media the oxidation proceeds as pictured in Scheme I, *via* steps e and f, and involves the consumption of one iodine molecule and the generation of two iodide ions. Step f requires proton elimination and thus it should be favored in basic media and inhibited in acidic media. We suggest that in the latter circumstance a second iodination reaction, h, to form 6, may participate, resulting in the overconsumption of iodine, as was observed in the rapid-titration experiment at pH 5. However, when the titration at acid pH is carried out slowly, an additional pathway, which is opposed to iodine overconsumption, becomes operative. Thus, the iodide ion generated by steps e and f can, at acid pH, attack the protonated diaziridine 4 resulting in ring scission to 7 with ultimate hydrolysis through 8 to cyclohexanone 1, and the concommitant generation of iodonium ion. The formation of iodonium ion establishes a catalytic process (reactions e and f, then d, i, and j) and, to the extent that this process can assert itself, underconsumption of iodine will result.

SCHEME II



Although no concrete evidence can be presented for the existence of 6,[8] its presence for a finite time would allow overconsumption of iodine to occur as long as iodine elimination from it is sufficiently slower than the rate of its formation. However, the lifetime of 6 must be relatively short under the conditions of the cyclic process; otherwise iodine concentration would be reduced and the catalytic reaction would be slowed or stopped.

We have previously noted that the conversion of ketones to N,N′-unsubstituted diaziridines is subject to

(4) Silver mirrors produced by Tollens reagent, as well as the reagent itself, are notoriously explosive, probably owing to reaction of silver ion and ammonia. Since similar conditions are potentially present in diazirine preparations with silver oxide, prudence dictates that they be avoided, particularly on a large scale.

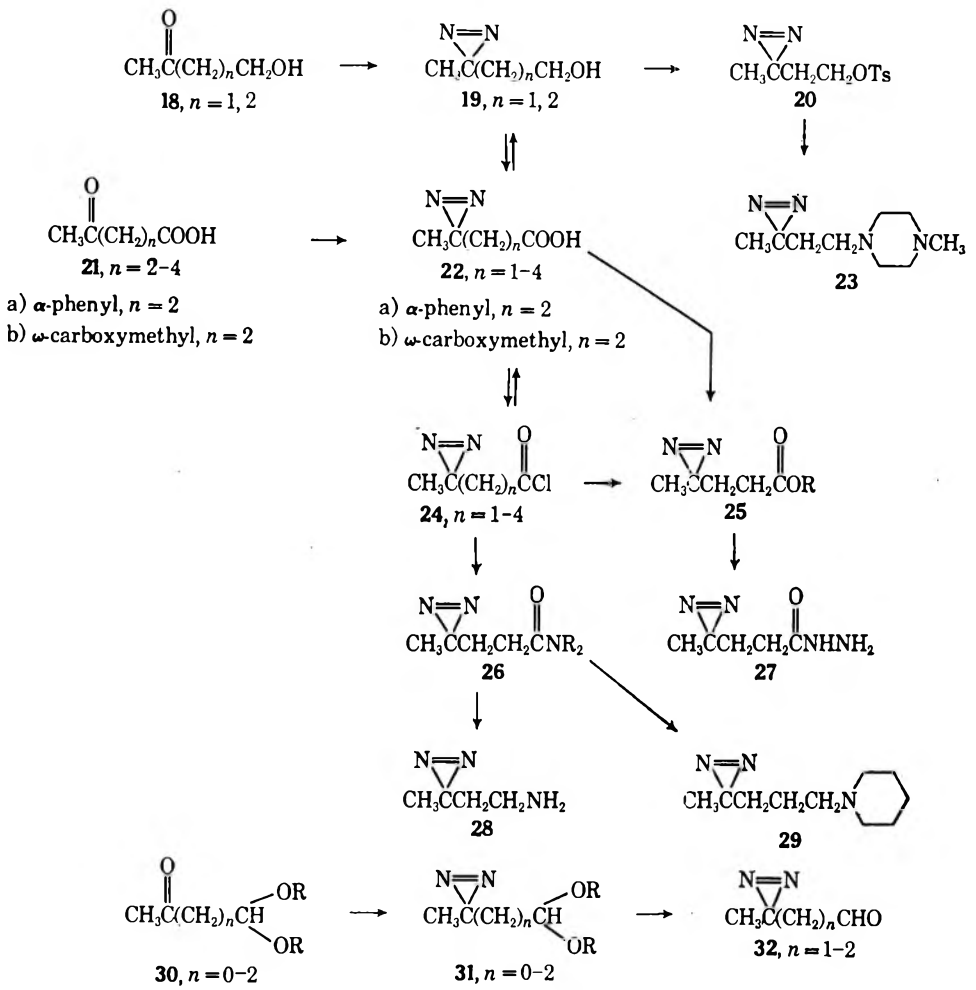
(5) H. Kato and M. Ohta, *Bull. Chem. Soc. Jap.*, **35**, 2048 (1962).

(6) Ammonia can be removed completely by partial evaporation of the methanolic reaction medium (in the case of carboxylic acids, one equivalent of triethylamine is added prior to evaporation of ammonia). If nitrogen triiodide is indeed formed as a result of incomplete removal of ammonia, it can be detected as an insoluble silvery black precipitate.

(7) E. Schmitz, R. Ohme, and R. D. Schmidt, *Chem. Ber.*, **95**, 2714 (1962).

(8) See R. A. Mitsch, *J. Heterocycl. Chem.*, **3**, 245 (1966), for the preparation of 3,3-difluorodiazirine (ii) from bis(difluoramino)difluoromethane through related intermediate i. Also see W. H. Graham, *J. Org. Chem.*, **30**, 3108 (1965), for a discussion of species such as iii, which are postulated as intermediates, for example, in the reaction of dichloramine with imines to prepare diazirine.

SCHEME III



serious electronic and steric restrictions.[1] For example, α,β unsaturation, or an adjacent *gem*-dimethyl group, prevents reaction with steroid 3-ketones,[1] and acetophenone affords a diaziridine by an indirect reaction in only 9% yield.[2c,9,10] The present investigation further confirms the observation that this reaction of ketones with ammonia and hydroxylamine-O-sulfonic acid is not generally applicable. Thus, we were unable to effect the transformation of cyclopentanone,[11] quinuclidin-3-one, and dicyclopropyl ketone to the corresponding diazirines. Furthermore, attempts to convert tropinone (**9**, X = NCH_3) to the diazirine (**11**, X = NCH_3) gave only the oxime **12**, despite the fact that the 8-thia analog **13** (X = S) is reported[12] to afford the diazirine **14** (X = S) in relatively good yield (Scheme II). Also, the reaction with cyclohexane-1,4-dione **15** failed to yield the bisdiazirine **16**; after numerous attempts we could isolate only 4,4-azocyclohexanone oxime (**17**) in 1–2% yield.

Nevertheless, a considerable variety of relatively simple ketones bearing other functional groups can be smoothly converted to the corresponding diazirines (see Scheme III and Table I). The homologous series of keto alcohols **18**[13] and keto acetals **30** readily undergo this transformation. The homologous series of keto acids **21** ($n > 1$) also afford the diazirines **22** ($n > 1$), but, when the conversion of **21** ($n = 1$) was attempted, no diazirine was obtained. This diazirine acid (**22**, $n = 1$) is, however, available by chromic acid oxidation[14] of the diazirine alcohol **19** ($n = 1$).

The diazirine function is compatible with a variety of reagents, so that transformation of the other functional group proceeds cleanly affording additional types of diazirine-containing molecules. Thus, the azobutanol **19** ($n = 1$) was converted to the tosylate **20**, which in turn reacted smoothly with N-methylpiperazine to give amine **23**. Similarly, the acids **22** provided the corresponding acid chlorides **24**,[15] useful for the preparation of esters, *e.g.*, **25** (R = benzyl) and amides **26**. Fisher esterification of acid **22** ($n = 2$) afforded ester **25** (R = methyl).[15] Incidentally, the acid chlorides could be obtained directly from crude diazirine acid preparations. They constituted useful intermediates for the purification of the diazirine acids, since the boiling ranges of the acid chlorides allowed lower distillation temperatures and, therefore, much less thermal decomposition. Recovery of the acid by

(9) Extensive review: E. Schmitz, *Advan. Heterocycl. Chem.*, **2**, 83 (1963).

(10) Schiff base iv reacts with monomethylamine and hydroxylamine-O-sulfonic acid to yield 1-methyl-3-phenyldiaziridine in 77% yield,[3a] but this compound is not a diazirine intermediate.

PhCH=N—CH_3

iv

(11) This observation parallels our finding[1] that certain steroid 17-ketones are unreactive.

(12) J. J. Eubel and J. C. Martin, *J. Amer. Chem. Soc.*, **86**, 4618 (1964).

(13) See E. Schmitz, C. Horig, and C. Grundemann, *Chem. Ber.*, **100**, 2093 (1967), for the preparation and properties of a series of α-hydroxydiazirines.

(14) F. L. M. Pattison, J. B. Stothers, and R. B. Woolford, *J. Amer. Chem. Soc.*, **78**, 2255 (1956).

(15) For additional examples, see ref 3.

TABLE I
DIAZIRINES PREPARED DIRECTLY FROM KETONES

Compd no.	Structure	Method of oxidation[a]	Yield from ketone	bp (mm) or mp (solvent)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Principal ir bands,[b] μ	Uv bands,[c] mμ (ε)	Nmr terminal methyl absorption, δ
22, n = 2	$CH_3C(N=N)(CH_2)_2COOH$	A[d] B	42 43	66 (0.12) 8.5–10 (hexane)	46.87	6.29	21.87	46.76	6.38	21.94	3.30 (m), 5.83 (s), 6.32 (w), A	347 (64), 363 (52)	1.05
22, n = 3	$CH_3C(N=N)(CH_2)_3COOH$	B	38	14–16 (hexane)	50.69	7.09	19.71	51.06	7.26	19.52	3.25 (s), 5.84 (s), 6.26 (m), A	348 (57), 365 (50)	
22, n = 4	$CH_3C(N=N)(CH_2)_4COOH$	A[d]	30	8–10 (hexane)	53.84	7.74	17.94	54.15	7.40	17.58	3.3 (s, broad), 5.85 (s), 6.30 (m), B	350 (66), 366 (59)	
22a	$CH_3CC(N=N)CH_2CH(C_6H_5)COOH$	B	47	73.5–75 (methanol–water)	64.69	5.92	13.72	64.64	6.20	13.56	3.4 (m), 5.95 (s), 6.30 (w), C	346 (66), 361 (51)	
22b	$HOOCCH_2CH_2CC(N=N)CH_2CH_2COOH$	B	28	121–123 (water)	45.16	5.41	15.05	45.03	5.49	15.01	3.3 (s), 5.80 (vs), 5.85 (vs), 6.30 (m, sharp), 7.82 (s, sharp), 10.7 (s), D	345 (58), 362 (39)	
31, n = 0	$CH_3CC(N=N)CH(OC_2H_5)_2$	A B	41 40	37 (8)	53.14	8.92	17.71	53.48	9.12	18.30	3.47 (m), 6.25 (w), 9.0 (m), 9.4 (m, broad), A	331 (40), 341 (35)	1.07
31, n = 1	$CH_3CC(N=N)CH_2CH(OCH_3)_2$	A B	22 26	45 (12)	49.98	8.38	19.44	50.48	8.77	19.44	3.55 (m, sharp), 6.30 (m), 8.90 (s), 9.3–9.5 (s, broad), B	347 (58), 361 (46)	1.07
31, n = 2	$CH_3CC(N=N)CH_2CH_2CH(OC_2H_5)_2$	A	40	43 (2.5)	58.03	9.75	15.04	58.22	10.12	14.46	3.45 (s), 6.3 (m), 8.85 (s), 9.35 (s), B	348 (72), 365 (56)	
19, n = 1	$CH_3CC(N=N)CH_2CH_2OH$	A B	35 40	32 (3) 44 (6)	47.98	8.06	27.98	48.24	8.75	27.54	3.0 (s), 6.28 (s), 9.5 (s), B	347 (55), 365 (40)	1.04
19, n = 2	$CH_3CC(N=N)CH_2CH_2CH_2OH$	A	39	42 (2.5)	52.61	8.83	24.55	52.78	8.96	23.93	2.9 (s, broad), 6.28 (s), 9.5 (broad) 9.5, B	348 (63), 365 (51)	

[a] A, iodine–triethylamine oxidation; B, silver oxide oxidation. [b] A, $CHCl_3$ solution; B, film; C, Nujol mull; D, KBr disk. [c] In methanol solution. [d] In at least one experiment, the crude diazirine prepared by iodine oxidation was purified through the acid chloride. See text.

hydrolysis of the acyl halide was thence straightforward.

Amines could be obtained not only by displacement of the tosylate as previously mentioned, but also by application of the Hofmann hypobromite reaction (synthesis of **28**) and by diborane reduction of disubstituted amides (synthesis of **29**). However, diborane reduction of the unsubstituted amide **26** (R = H) was not successful because of concommitant reduction of the diazirine function. On the other hand, diborane reduction of the carboxylic acid group was sufficiently rapid to allow the clean reduction of **22** (n = 2) to the diazirine alcohol **19** (n = 2).

The homologous series of acetals **31** could be transformed to the corresponding diazirine aldehydes **32** when $n > 0$. However, **31** (n = 0) was inert to dilute acid, as in the corresponding keto acetal **30** (n = 0).

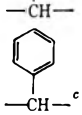
In general, the various diazirines were found to be stable to storage of several months or longer, the only exceptions being the C_4 and C_5 acids **22** (n = 1, 2), which darkened considerably and partially liquefied even when stored at −10° in the solid state.

The electron-withdrawing character of the diazirine group is apparent when the pK_a of a series of diazirine acids is considered (see Table II). The effect on the

TABLE II

EFFECT OF THE DIAZIRINE GROUP AND OTHER REPRESENTATIVE FUNCTIONAL GROUPS ON THE pK_a[a] OF ALIPHATIC ACIDS

CH_3—X—$(CH_2)_n$—COOH

	pK_a			
X	n = 1	2	3	4
CH_2	4.8	4.8	4.8	4.8
	3.9	4.4[b]	4.5	4.7
	3.6	4.6	4.8	
	4.2	4.4	4.6	
	4.4	4.7	4.8	

[a] The pK_a's were determined by titration in aqueous solution at 25°. [b] The pK_a of compound **22a**, containing an α-phenyl group, is 3.9. [c] The pK_a of α-phenylpropionic acid is 4.3.

carboxylic acid proton is roughly comparable with that exerted by a keto group or a chlorine atom, and is still detectable through three and possibly four intervening methylene groups. (It is interesting that, in one instance, 4,4-azo-2-phenylpentanoic acid (**22a**), a cumulative effect obtains when the acid is substituted by both an α-phenyl and a γ-azo function.) A further manifestation of this electron-withdrawing effect is observed by comparison of 1-amino-3,3-azobutane hydrochloride (**28** HCl salt, pK_a = 9.35) with 1-aminobutane hydrochloride (pK_a = 10.7). Probably the inability to hydrolyze the azo acetal **31** (n = 0) in the presence of dilute acid can also be attributed to this effect.

The weak, but characteristic, ultraviolet absorption of the diazirine group occurs as a double peak at 351 ± 1 mμ and 368 ± 2 mμ.[1] We have noted a hypsochromic shift of up to 27 mμ in the presence of neighboring electron-withdrawing groups, the effect diminishing rapidly as more than one methylene group intervenes between the functions. In the infrared, these groups cause a weak hypsochromic shift (at most 0.04 μ) of the diazirine absorption. The reciprocal effect by the diazirine function on the neighboring groups is even weaker. These infrared effects disappear entirely with the intervention of more than one methylene group.

In previous reports,[1,12] it was shown that the diazirine group exhibits a very high degree of magnetic anisotropy. This effect does not carry over to the more flexible noncyclic aliphatic series. In fact, relative to methylene, the diazirine function exhibits virtually no shielding or deshielding effect on adjacent methyl groups, resonance for the protons of which was noted at δ 1.05 ± 0.02 [four out of five examples; in the fifth, 3,3-azobutanal (**32**, n = 1), it was at 1.15].

Experimental Section

General.—Melting points were measured in a Mel-Temp apparatus in open capillary tubes and are corrected. Ultraviolet spectra were determined with a Cary recording spectrophotometer (Model 14), and infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Nmr spectra were obtained on a Varian Model A-60 spectrometer in deuteriochloroform using tetramethylsilane as internal standard. Solutions were dried with anhydrous sodium sulfate except where noted and evaporations were carried out at reduced pressure. Boiling points are uncorrected.

Oxidation of 1,1-Hydrazicyclohexane (2). Titration with Iodine.—The direct titrations of 1,1-hydrazicyclohexane were carried out in appropriately buffered aqueous solutions using 0.094 N methanolic iodine solution at 24°. The pH's of the solutions were determined at the beginning and end of the titrations and were found to vary not more than 0.4 pH units, becoming progressively more acidic. The titrations were followed either by the appearance of a persistent iodine color (using starch indicator) or potentiometrically using a platinum electrode *vs.* a calomel electrode.

For the study of the catalytic process, appropriately buffered aqueous solutions of 1,1-hydrazicyclohexane were treated with 0.05 mol equiv of iodine at 24°, aliquots were removed and made strongly basic with aqueous sodium hydroxide, and the remaining diaziridine was titrated potentiometrically using 0.094 N methanolic iodine solution. After correction for the immediate rapid consumption of 0.05% of the initial diaziridine, the disappearance of diaziridine follows first-order kinetics. The results are summarized in Tables III and IV.

TABLE III

TITRATION OF 1,1-HYDRAZICYCLOHEXANE (2)

Expt no.	pH	Elapsed time for titration, min	Mol equiv of I_2 consumed
1	11.0	30+	0.99
2	11.0	3	1.00
3	8.9 ± 0.1	30+	1.00
4	8.9 ± 0.1	3	1.01
5	6.5 ± 0.2	30+	0.85
6	5.0 ± 0.1	7	0.62
7	5.0 ± 0.1	5	0.77
8	5.0 ± 0.1	2.0	1.10
9	5.0 ± 0.1	1.5	1.15

General Method for the Synthesis of Diazirines. Synthesis of 3,3-Hydrazibutanol-1.—A solution of 11.2 g (0.13 mol) of 3-ketobutanol-1 (**18**, n = 1) in 200 ml of liquid ammonia was stirred for a 5-hr period at reflux temperature. The solution was then cooled in a Dry Ice–acetone bath and a solution of 16 g (0.15 mol) of hydroxylamine-O-sulfonic acid in 100 ml of methanol was added over a 30-min period. The cooling bath was removed, the mixture was stirred at reflux (Dry Ice condenser) for about an hour, and the ammonia was allowed to evaporate overnight. The

TABLE IV

RATE OF DISAPPEARANCE OF DIAZIRIDINE AT 24° USING 0.05 MOL EQUIV OF I_2

Expt no.	pH	Catalyst	Mol equiv	Time, min	Mol of diaziridine remaining
1	2.6 ± 0.1	I_2	0.05	0.0	0.585
				0.7	0.36
				1.5	0.25
				2.5	0.17
				5.0	0.055
				10.0	0.01
2	5.0 ± 0.2	I_2	0.05	0.0	0.59
				2	0.47
				5	0.38
				10	0.24
				20	0.132
				30	0.06
3	6.8 ± 0.1	I_2	0.05	0	0.59
				5	0.56
				20	0.55
				80	0.52
				125	0.50
4	9.1	I_2	0.05	0	0.58
				10	0.56
				20	0.56
				100	0.55
5	5.0 ± 0.2	KI	0.8	0	0.54
				5	0.03
6	5.0 ± 0.2	KI	0.1	0	0.54
				5	0.26
				20	0.03

resulting slurry was filtered and the filter cake was washed with several portions of methanol. All washings were combined with the original filtrate and the solution (about 200 ml) was concentrated to about 60 ml; no odor of ammonia could be detected. The 3,3-hydrazibutanol thus prepared was oxidized without further work-up.

Preparation of Diazirines by Oxidation of Diaziridines. Method A. With Iodine–Triethylamine. Synthesis of 3,3-Azobutanol-1 (19, $n = 1$).—The crude methanolic solution of 3,3-hydrazibutanol-1 (prepared as described above from 40 g, 0.45 mol, of 3-ketobutanol-1) was diluted with 200 ml of methanol, cooled in an ice bath, and treated with 60 ml of triethylamine; this was followed by addition of solid iodine at a rate of ~1 g/min. Iodine reduction was virtually instantaneous. After 68 g (0.27 mol) of iodine had been added, the red color of excess iodine persisted. The solution was concentrated to about 250 ml and then diluted to about 800 ml with brine. The solution was extracted with several portions of ether, and the combined extracts were dried and concentrated to about 50 ml. The residue was distilled, yielding 16.0 g (35%) of 3,3-azobutanol-1 (19, $n = 1$) with bp 32° (0.3 mm).

Method B. Oxidation with Silver Oxide.—The methanolic solution of 3,3-hydrazibutanol-1, prepared as described above, was added with stirring and ice cooling during 10 min to a suspension of silver oxide in water (freshly prepared by the addition of a solution of 34 g of silver nitrate in 100 ml of water to 200 ml of 4% aqueous sodium hydroxide). The resulting slurry was filtered through Celite[16] and the filtrate was treated with brine. The precipitated silver chloride was removed by a second filtration through Celite.[16] The colorless solution was extracted with several portions of ether and methylene chloride. The combined extracts were concentrated to about 40 ml and the residue was distilled, yielding 5.14 g (40%) of 3,3-azobutanol-1 with bp 42.5–44° (5.5–6 mm). This material was spectroscopically identical with that prepared by method A.

Tropinone Oxime (12). **Attempted Preparation of 5,5-Azotropane** (13, X = NCH_3).—A solution of 6.21 g of tropinone (11, X = NCH_3) in 20 ml of methanol was added to 40 ml of liquid ammonia and stirred at reflux for 1.5 hr. The solution was then treated with 13.2 g of hydroxylamine-O-sulfonic acid as described above for the preparation of diaziridines to give a brown oil which on partition chromatography afforded 740 mg of a single crystalline product, recrystallized from methylene chloride–hexane to yield 592 mg of tropinone oxime as short blunt needles: mp 111–113°;[17] uv end absorption only; ir (KBr) 3.38, 3.55, 6.04 (weak), 9.94, 10.70, 13.25 μ.

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.14; N, 18.17; mol wt, 154. Found: C, 61.98; H, 9.42; N, 17.94; mol wt, 170 ($CHCl_3$).

A 3-g sample of the crude mixture oxidized by method B of the general procedure afforded 8 mg of tropinone, mp 40–41°, as the only characterizable product.

4,4-Azocyclohexanone Oxime (17).—A solution of 890 mg of cyclohexane-1,4-dione (15) was added to 100 ml of methanol saturated at 0° with ammonia, and the solution was stirred 1.5 hr at 0° ± 2°. A solution of 1.80 g of hydroxylamine-O-sulfonic acid in 10 ml of methanol was added dropwise and the resulting solution was stirred 2.5 hr at 0° and filtered. The filtrate was evaporated to a volume of about 50 ml and oxidized according to oxidation method B. The oily residue obtained after evaporation of the solvent was chromatographed on 7 g of silica gel. Elution with 150 ml of 5% ether in benzene afforded 66 mg (5.4%) of product, which was recrystallized from ether–hexane in fine needles, 23 mg, mp 88–89°. The compound is polymorphic, the needles initially obtained slowly changing to sugar-like crystals: mp 87–98°; uv λ_{max}^{MeOH} 347 mμ (ε 97), 362 (83); ir (KBr) 3.15, 3.25, 6.0, 6.34 μ.

Anal. Calcd for $C_8H_9N_3O$: C, 51.78; H, 6.52; N, 30.20. Found: C, 52.15; H, 6.57; N, 30.30.

4,4-Azopentanol-1 (19, $n = 2$) **(by Diborane Reduction of 4,4-Azopentanoic Acid).**—A stirred solution of 918 mg of 4,4-azopentanoic acid (22, $n = 2$) in 35 ml of dry tetrahydrofuran was treated dropwise with 5 mmol of diborane in tetrahydrofuran. The resulting solution was stirred at room temperature for 0.5 hr, water was added cautiously to destroy excess reagent, and the solution was diluted with brine. The layers were separated and the aqueous layer was extracted with two small portions of ether. The combined organic portions were washed with aqueous sodium bicarbonate and brine, then dried, and evaporated. The residue was distilled, yielding 306 mg of a colorless, mobile liquid with bp 61° (5 mm). This product was spectroscopically identical with that prepared from 4-ketopentanol-1 (18, $n = 2$) by the general method described for the preparation of diazirines (Table I).

3,3-Azo-1-(*p*-toluenesulfonyloxy)butane (20).—A solution of 10.1 g of 3,3-azobutanol-1 (19, $n = 1$) in 80 ml of pyridine was cooled and 20 g of *p*-toluenesulfonyl chloride was added in portions. The solution was stirred at 0–10° for 2 hr and allowed to stand at 4° for 16 hr, and poured into a mixture of 150 ml of concentrated hydrochloric acid and 600 g of ice. The oily layer was extracted into ether and the ethereal extract was washed with cold dilute hydrochloric acid, cold dilute sodium hydroxide, and brine and then dried. After evaporation of the ether, the residue was recrystallized from ether–petroleum ether to afford 17.55 g (70%) of product with mp 25.5–28°; uv λ_{max}^{MeOH} 225 mμ (ε 1200), 256–273 (multiplet, 400–550), 342 (75), 360 (57); ir (KBr) 6.25, 8.42, 8.5, 10.3, 11.1, 15.2 μ.

Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.96; H, 5.55; N, 11.02; S, 12.59. Found: C, 51.65; H, 5.70; N, 11.02; S, 12.26.

N-Methyl-N′-(3,3-azobutyl)piperazine (23).—A solution of 5 g of 3,3-azo-1-(*p*-toluenesulfonyloxy)butane (20) and 4 ml of N-methylpiperazine in 40 ml of dimethylformamide was heated at 82° ± 2° for 6 hr, then held 16 hr at room temperature. The solution was diluted with 150 ml of water, acidified (HCl) to congo red, and extracted with ether. The aqueous phase was made strongly basic (NaOH) and extracted with several portions of ether. The combined extracts were dried (KOH), the ether was evaporated, and the residue was distilled, the fraction boiling at 33–50° (2–15 mm) being collected. Redistillation, 47° (2 mm), afforded 1.48 g (40%) of amine 23: uv λ_{max}^{MeOH} 349 mμ (ε 55), 364 (37); ir (neat) 3.40, 3.56, 6.26, 7.80, 8.60, 9.90 μ.

Anal. Calcd for $C_9H_{18}N_4$: C, 59.34; H, 9.89; N, 30.86. Found: C, 59.64; H, 9.70; N, 30.08.

3,3-Azobutyric Acid (22, $n = 1$).—To a solution of 16 g of chromic acid in 180 ml of acetic acid–water (5:1) at 3° was added dropwise 7.0 g of 3,3-azobutanol-1 (19, $n = 1$). The solution was stirred 45 min at 3°, then at room temperature overnight. The solution was diluted with 500 ml of brine and extracted with

(16) Celite is the trademark of the Johns–Manville Co. for diatomaceous earth silica products.

(17) Lit. 110–111°: E. Otiai, K. Tuda, and K. Murakami, *J. Pharm. Soc. Jap.*, **57**, 407 (1937).

several portions of ether. The combined extracts were washed once with brine and the solvent was evaporated. The residue was distilled to afford 2.8 g (35.1%) of product with bp 44° (0.15 mm) as a yellow liquid. Redistillation, 48° (0.18 mm), afforded a colorless oil that crystallized at −20°: mp −2–3°; uv λ_{max}^{MeOH} 343 mμ (ε 66), 359 (51); ir (neat) 3.3, 5.80, 6.26 μ. This material is unstable, becoming yellow after standing at room temperature for several hours. Storage for several weeks in the solid state at −10° affords a bright yellow oily solid.

Anal. Calcd for $C_4H_6N_2O_2$: C, 42.10; H, 5.30; N, 24.55. Found: C, 43.88; H, 6.19; N, 23.48.

4,4-Azopentanoyl Chloride (24, n = 2).—A solution of 12.4 g of 4,4-azopentanoic acid (**22**, n = 2) and 15.4 g of oxalyl chloride was allowed to stand for 16 hr protected from atmospheric moisture. The solution was distilled, affording 12.4 g (88%) of product with bp 38° (5 mm); uv λ_{max}^{hexane} 341 mμ (ε 84), 358 (80); ir (neat) 5.57, 5.78, 6.3 μ.

Anal. Calcd for $C_5H_7ClN_2O$: C, 40.97; H, 4.81; Cl, 24.17; N, 19.11. Found: C, 41.11; H, 4.90; Cl, 24.15; N, 19.28.

Basic aqueous hydrolysis of this acyl halide afforded a 90% yield of 4,4-azopentanoic acid, identical by boiling point, melting point, and spectral data with the starting 4,4-azopentanoic acid.

Methyl 4,4-Azopentanoate (25, R = CH_3).—A solution of 8.0 g of 4,4-azopentanoic acid (**22**, n = 2) in 50 ml of methanol was treated with hydrogen chloride and allowed to stand for 16 hr. The solution was poured into dilute sodium bicarbonate solution and extracted with ether. The combined extracts were washed ($NaHCO_3$) and dried. After evaporation of the solvent, the residue was distilled to afford 6.26 g of ester having bp 45° (5.5 mm); uv λ_{max}^{MeOH} 346 mμ (ε 60), 362 (50); ir (neat) 5.75, 6.32, 8.35, 8.50 μ.

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 51.03; H, 7.36; N, 19.46.

4,4-Azopentanamide (26, R = H).—To 160 ml of concentrated ammonium hydroxide at 0° was added slowly with good stirring 17.5 g of 4,4-azopentanoyl chloride (**24**, n = 2), the temperature being kept below 10°. The resulting mixture was extracted with methylene chloride; the extracts were washed with brine and evaporated. The crystalline residue was recrystallized from methylene chloride–hexane to afford 11.9 g of the product: mp 89.5–91°; uv λ_{max}^{MeOH} 348 mμ (ε 64), 363 (55); ir (KBr) 2.97, 6.02, 6.11, 6.35 μ (shoulder).

Anal. Calcd for $C_5H_9N_3O$: C, 47.23; H, 7.13; N, 33.06. Found: C, 47.04; H, 7.12; N, 33.11.

N-(4,4-Azopentanoyl)piperidine [26, $(R)_2$ = $(CH_2)_5$].—To an ice-cooled solution of 5 g of 4,4-azopentanoyl chloride (**24**, n = 2) in 300 ml of benzene was added dropwise 10 ml of piperidine with the temperature maintained below 25°. The mixture was stirred 16 hr, then treated with 60 ml of water, and shaken well; the layers were separated. The organic phase was washed twice with 2 *N* hydrochloric acid and once with dilute sodium bicarbonate and dried. After evaporation of the solvent, the residue crystallized at Dry Ice temperature and was recrystallized from petroleum ether at −20 to −60° to afford 5.25 g of fine needles, with mp 9–11° after drying at high vacuum.

Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.77; N, 21.53. Found: C, 61.16; H, 8.95; N, 21.14.

4,4-Azopentanoyl Hydrazide (27).—A solution of 4.5 g of hydrazine hydrate in 25 ml of methanol was refluxed while 6.8 g of methyl 4,4-azopentanoate (**25**, R = CH_3) was added dropwise over a 40-min period. The solution was stirred 30 min at reflux and concentrated at 85° (0.5 mm) to a yellow oil. Upon cooling, the oil solidified to a waxy solid with mp 39–40° (no satisfactory solvent for recrystallization was found); uv λ_{max}^{MeOH} 346 mμ (ε 57), 363 (43); ir (KBr) 3.30, 3.40, 6.0 μ (broad).

Anal. Calcd for $C_5H_{10}N_4O$: C, 42.24; H, 7.09; N, 39.42. Found: C, 41.56; H, 7.23; N, 36.85.

The maleate salt was recrystallized from ethanol–ether to afford white crystals, mp 90–92°.

Anal. Calcd for $C_9H_{14}N_4O_5$: C, 41.85; H, 5.47; N, 21.70. Found: C, 42.18; H, 5.77; N, 21.23.

1-Amino-3,3-azobutane HCl (28).—To a solution of sodium hypobromite (prepared by adding 12.50 g of bromine to 100 ml of 3 *N* sodium hydroxide at 5°) was added 6.22 g of 4,4-azopentanamide (**26**, R = H). The solution was stirred 2.5 hr at 0–20°, then warmed slowly to 45°, at which temperature a mild exothermic reaction began, the temperature rising to 60°. The solution was distilled and the distillate (about 20 ml) was collected in 20 ml of 3 *N* hydrochloric acid. The distillate was made strongly basic (NaOH) and extracted with several portions of ether. Treatment of the dried ethereal solution with hydrogen chloride afforded the product as thin glistening plates, 2.49 g (34%), with mp 170–172°; uv λ_{max}^{MeOH} 344 mμ (ε 58), 360 (48); ir (KBr) 3.35, 6.3 μ.

Anal. Calcd for $C_4H_{10}ClN_3$: C, 35.43; H, 7.43; N, 30.99. Found: C, 35.84; H, 7.81; N, 30.61.

N-(4,4-Azopentyl)piperidine (29).—To 16.7 ml of 1 *M* sodium borohydride in tetrahydrofuran cooled in Dry Ice–acetone was added 1.95 g of N-(4,4-azopentanoyl)piperidine [**26**, $(R)_2$ = $(CH_2)_5$] in 10 ml of dry tetrahydrofuran. The temperature remained between 0 and 6° throughout. When the addition was complete, the solution was refluxed 20 min, then cooled in ice, and treated carefully with 2.5 ml of 6 *N* hydrochloric acid. The solution was warmed briefly, diluted with 50 ml of water, made strongly acidic (HCl), and extracted with several small portions of ether. After evaporation of the solvent, the residue was added to 40 ml of 1 *N* hydrochloric acid and the solution was heated on the steam bath for 1.5 hr. The cooled solution was extracted with ether, then made strongly basic with solid sodium hydroxide, and extracted with ether. The dried ethereal extracts were evaporated, and the residue was distilled, yielding 338 mg of the product (18.6%): bp 60–62° (3 mm); uv λ_{max}^{MeOH} 349 mμ (ε 59), 365 (95).

Anal. Calcd for $C_{10}H_{19}N_3$: C, 66.25; H, 10.57; N, 23.18. Found: C, 66.66; H, 10.78; N, 23.07.

3,3-Azobutyraldehyde (32, n = 1).—A solution of 4.86 g of 3,3-azo-1,1-dimethoxybutane (**31**, n = 1) and 0.5 ml of concentrated hydrochloric acid in 30 ml of acetone–water (3:1) was allowed to stand 16 hr at room temperature. The solution was saturated with salt and extracted with ether. The extracts were washed with brine, dried, and evaporated. The residue was distilled, affording 2.0 g (65.2%) of aldehyde, bp 45–56° (35 mm). Redistillation at 49–49.5° (37 mm) afforded a pure sample: uv λ_{max}^{MeOH} 344 mμ (ε 25), 360 (20); ir (neat) 5.77, 6.27 μ; nmr δ 1.15 (CH_3–).

Anal. Calcd for $C_4H_8N_2O$: C, 48.97; H, 6.16; N, 28.55. Found: C, 49.64; H, 7.36; N, 26.30.

The semicarbazide of 3,3-azobutyraldehyde had mp 103–104.5°.

Anal. Calcd for $C_5H_9N_5O$: C, 38.70; H, 5.85; N, 45.14. Found: C, 38.73; H, 6.00; N, 45.24.

Registry No.—**12**, 1515-26-0; **17**, 25055-81-6; **19**, n = 1, 25055-82-7; **19**, n = 2, 16297-94-2; **20**, 25055-84-9; **22**, n = 1, 16297-95-3; **22**, n = 2, 25055-86-1; **22**, n = 3, 16297-97-5; **22**, n = 4, 25080-63-1; **22a**, 16297-96-4; **22b**, 16297-98-6; **23**, 25055-89-4; **24**, n = 2, 25055-90-7; **25**, R = CH_3, 25055-91-8; **26**, R = H, 25055-92-9; **26**, $(R)_2$ = $(CH_2)_5$, 25055-93-0; **27**, 25055-94-1; maleate salt of **27**, 25062-48-0; **28**, 25055-95-2; **29**, 25055-96-3; **31**, n = 0, 25055-97-4; **31**, n = 1, 25055-98-5; **31**, n = 2, 23902-18-3; **32**, n = 1, 25056-00-2; semicarbazide of **32**, n = 1, 25056-01-3.

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Studies in the Aziridine Series. Reactions of *trans*-1,3-Dibenzoyl-2-phenylaziridine and Related Systems[1]

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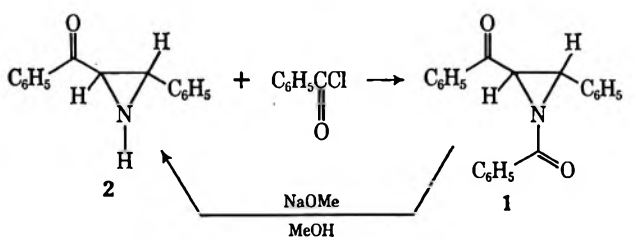
trans-1,3-Dibenzoyl-2-phenylaziridine (1) undergoes thermal rearrangement to 1,4-diphenyl-4-benzoyloxy-2-azabutadiene (14) *via* carbon–carbon bond cleavage of the aziridine ring. The inability of an external trapping reagent to trap the 1,3-dipole intermediate suggests that either the isomerization is a concerted process or else the 1,3 dipole rearranges faster than it can be trapped. The reactions of 1 with acid, base, and sodium iodide have also been investigated. The details of each reaction are described and evidence is presented demonstrating the existence of transient intermediates.

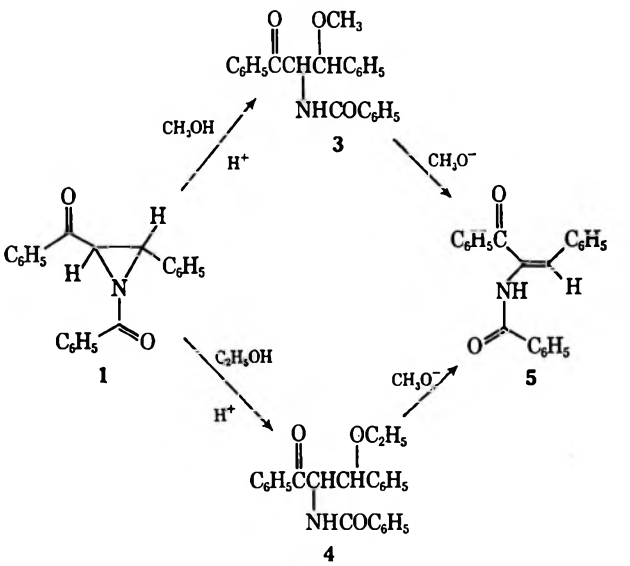
The thermal and photochemical behavior of small-membered nitrogen heterocycles has been the subject of recent reports from these laboratories.[3,4] Of specific interest has been the photochemistry of the 2-aroylaziridine system. Investigations of this ring system have shown that the nature and position of the substituents about the ring may produce markedly different chemical effects.[4] In order to accurately assess the electronic effects of substituents attached to the nitrogen atom, the photochemistry of a N-benzoyl substituted aziridine was undertaken.[5] Attempts to prepare and characterize a representative example of this system, *i.e.*, *trans*-1,3-dibenzoyl-2-phenylaziridine (1), led to the discovery of a large number of new ground-state transformations of this ring system. Our interests in the effects of substitution on the stability and chemistry of the aziridine ring motivated our investigation of these new reactions. The present paper describes the results of our studies.

trans-1,3-Dibenzoyl-2-phenylaziridine (1) was prepared by the reaction of *trans*-2-phenyl-3-benzoylaziridine (2) with benzoyl chloride in benzene. The assignment of structure 1 was supported by its elemental analysis, spectroscopic data (see Experimental Section), and hydrolysis of the material with sodium methoxide in methanol to 2 and methyl benzoate.



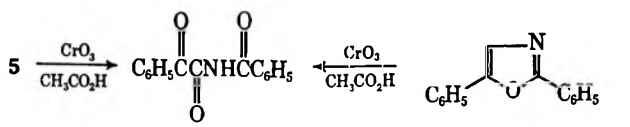
2 1

Treatment of 1 with methanol in the presence of a trace amount of acid led to the formation of 2-benzamido-1,3-diphenyl-3-methoxypropanone (3). A similar reaction with ethanol led to 2-benzamido-1,3-diphenyl-3-ethoxypropanone (4). Both of these compounds gave (α-benzamido)-*cis*-benzalacetophenone (5) when treated with base. Structure 5 was established by its elemental analysis, by spectroscopic data, and by



1 3 4 5

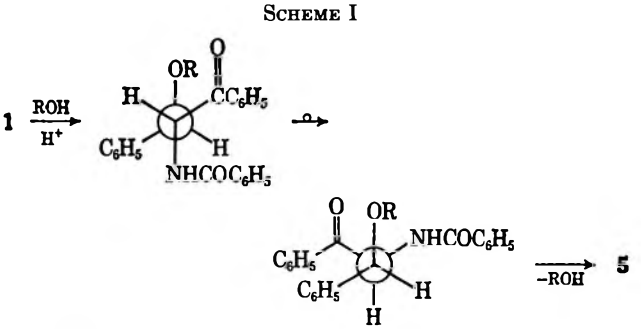
chemical degradation. Chromium trioxide oxidation of 5 in glacial acetic acid gave N-phenylglyoxylbenzamide (6), which could be prepared independently by the chromium trioxide oxidation of 2,5-diphenyloxazole. The oxidation of oxazoles are known to form N-phenylglyoxylbenzamides.[6] The *cis* relationship of the phenyl



6

and benzoyl groups is to be expected since the acid-catalyzed ring opening of the aziridine ring and the elimination of alcohol should occur in a stereospecific *trans* fashion (see Scheme I). We anticipated that a reaction

SCHEME I



1 5

(1) This work was presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969. For a preliminary report, see A. Padwa and W. Eisenhardt, *Chem. Commun.*, 1215 (1969).

(2) Alfred P. Sloan Foundation Fellow, 1968–1970.

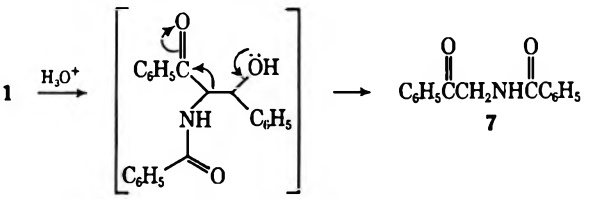
(3) A. Padwa and W. Eisenhardt, *ibid.*, **7**, 380 (1968); A. Padwa, L. Hamilton, and D. Eastman, *J. Org. Chem.*, **33**, 1317 (1968).

(4) A. Padwa and L. Hamilton, *J. Amer. Chem. Soc.*, **89**, 102 (1967); **87**, 1821 (1965). A. Padwa and W. Eisenhardt, *ibid.*, **90**, 2442 (1968).

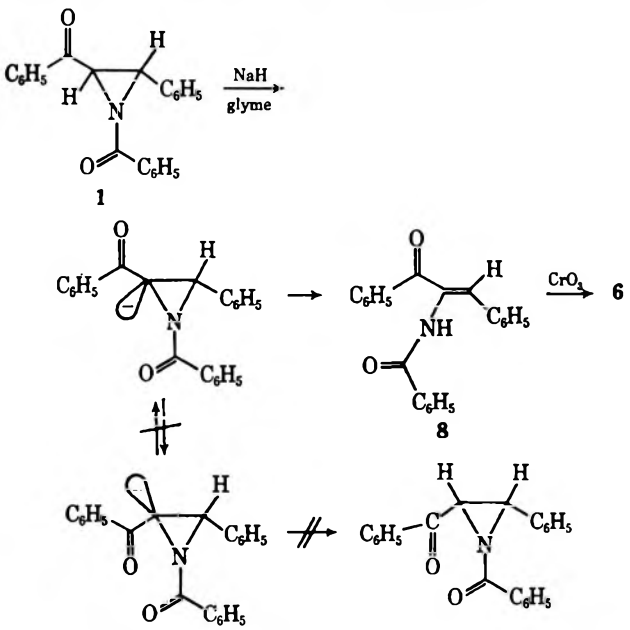
(5) The results of the photochemical studies will be reported at a later date.

(6) E. Fischer, *Ber.*, **29**, 209 (1896).

similar to that described above should occur upon treatment of **1** with aqueous acid. However, the initially produced 2-benzamido-1,3-diphenyl-3-hydroxypropanone underwent further fragmentation under the reaction conditions and gave N-phenacylbenzamide (**7**) and benzaldehyde.

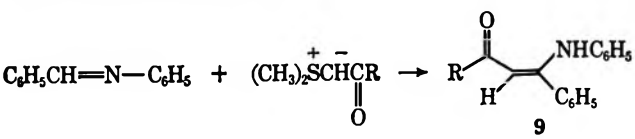


When a solution of **1** was treated with either sodium hydride or potassium *t*-butoxide, the isomeric (α-benzamido)-*trans*-benzalacetophenone (**8**) was isolated in excellent yield. The structure of **8** was confirmed by elemental analysis and by the oxidation of **8** to N-phenylglyoxylbenzamide (**6**). The mass spectra of **5** and **8** were virtually identical, although their nmr and infrared spectra were significantly different.

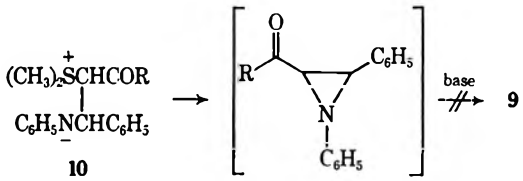


It is interesting to note that the ring opening of **1** to **8** occurred in a stereoselective manner. This implies that the aziridine ring is opened (to give **8**) faster than isomerization to the *cis* isomer. For the sake of completeness, we undertook a brief examination of the stability of **1** toward base isomerization. For short periods of time *trans*-aziridine **1** was recovered unchanged; no isomerization to the thermodynamically more stable *cis*-aziridine was detected.[7] Similarly, **5** was not isomerized to **8** (or **8** to **5**) under the base conditions.

The isolation of **8** from **1** is interesting in view of a recent publication concerning the reaction of benzalaniline with sulfonium ylides.[8] The major product of these reactions were cinnamic acid derivatives **9**. The

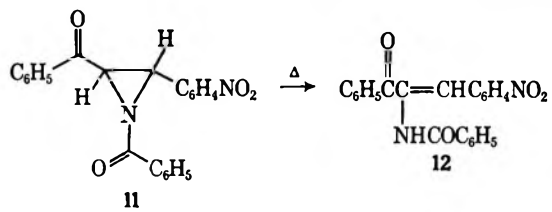


authors suggested that the initially formed betaine (**10**) underwent initial closure to an aziridine which rapidly opened to the observed product (**9**). From our results



it is clear that the base-catalyzed opening of a carbonyl aziridine gives an α-substituted benzalacetophenone derivative rather than the β-substituted isomer. We conclude, therefore, that the reaction of sulfonium ylides with imines does not involve the intermediacy of an aziridine. A similar conclusion has also been independently reached by Deyrup.[9]

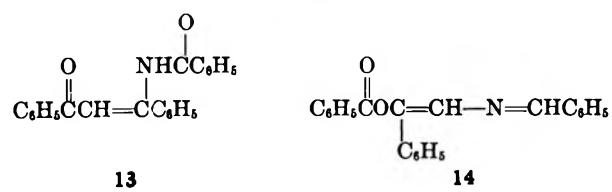
Heating a solution of **1** in benzene produced a single component in high yield (85%) that was shown to be isomeric with starting material. The thermal isomerization of the closely related nitroaziridine system (**11**) has been studied by Heine and Kaplan.[10] They reported that *trans*-1,3-dibenzoyl-2-*p*-nitrophenylaziridine (**11**) rearranged to α-benzamido-*p*-nitrobenzalacetophenone (**12**) when heated in an inert solvent.



It was suggested that the reaction proceeds by transfer of the aziridinyl hydrogen adjacent to the benzoyl group to the amido oxygen with concurrent breaking of the three-membered ring.

The isolation and characterization of *cis*- and *trans*-(α-benzamido)benzalacetophenone (**5** and **8**), however, eliminates this type of structure from further consideration as the thermolysis product of **1**.

Compounds **13** and **14** were also entertained as possible structures for the thermal product.

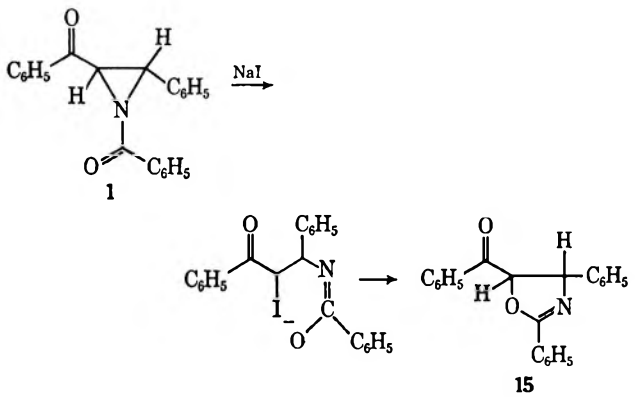


Compound **13** might be expected to arise by transfer of the aziridinyl hydrogen adjacent to the phenyl group to the amino oxygen followed by bond cleavage. This type of hydrogen transfer has been suggested to be important in the photochemistry of certain aroylaziridines[4] and perhaps strengthens the possible formation of compound **13** from the thermal reaction of **1**. Analysis of all the data enables us to reject structure **13** and indicates that structure **14** is the true structure of the thermal product.

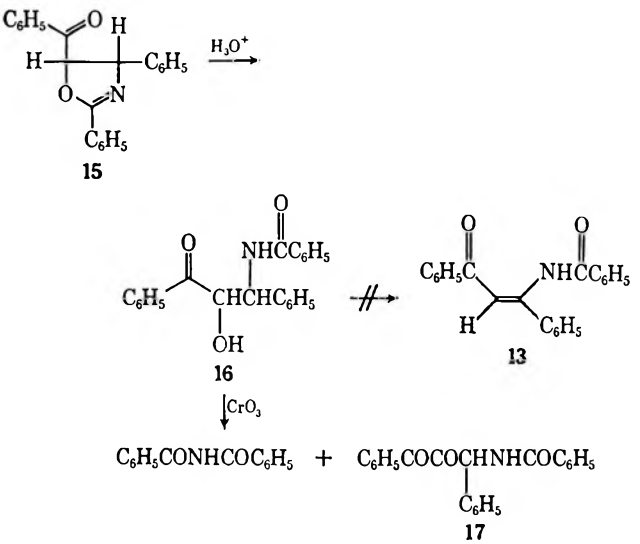
The isomerization of 1-acylaziridines into 2-aryl- or 2-alkyl-2-oxazolines by nucleophiles such as iodide ion

(7) R. E. Lutz and A. B. Turner, *J. Org. Chem.*, **33**, 516 (1968).
(8) A. J. Speziale, C. C. Tung, K. W. Ratts, and A. Yao, *J. Amer. Chem. Soc.*, **87**, 3460 (1965).
(9) J. A. Deyrup, *J. Org. Chem.*, **34**, 2724 (1969).
(10) H. W. Heine and M. S. Kaplan, *ibid.*, **32**, 3069 (1967).

has been extensively investigated in recent years.[11-15] The mechanism proposed for the isomerization involves initial attack by the nucleophile on an aziridinyl carbon to form a N-β-iodoethylbenzamido ion. In a subsequent step the ion cyclizes to the oxazoline and regenerates the iodide ion. When **1** was treated with sodium iodide in refluxing acetone the anticipated *trans*-2,4-diphenyl-5-benzoyl-2-oxazoline (**15**) was isolated.

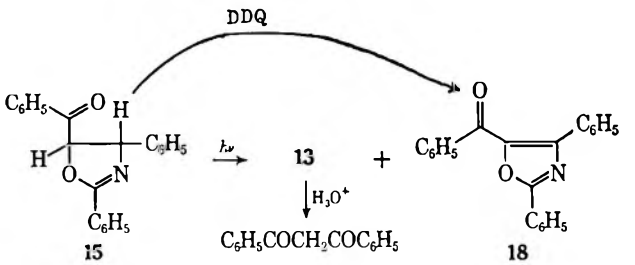


We intended to subject oxazoline **15** to acidic conditions so as to form N-1-phenyl-2-hydroxy-2-benzoylbenzamide (**16**). We hoped that compound **16** would in turn undergo dehydration to produce (β-benzamido)-*trans*-benzalacetophenone (**13**), a compound that was under consideration as the possible thermal rearrangement product of **1**.



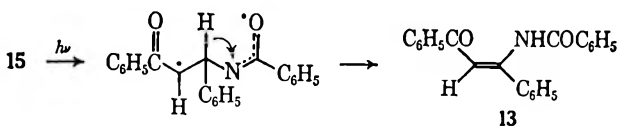
The conversion of **15** to **16** was in fact experimentally realized. Spectroscopic data and the further oxidation of **16** to dibenzamide and N-1-phenyl-1-phenylglyoxyl methylbenzamide (**17**) confirmed its structure. However, all attempts to dehydrate **16** to **13** have failed.

Although the desired β-benzamido-*trans*-benzalacetophenone (**13**) was not available from **16**, it occurred to us that the 5-benzoyl-2-oxazoline system (**15**) might serve as an alternate precursor to **13**. This observation might be achieved by photolytic rearrangement of **15**. In fact, irradiation of **15** in pentane afforded **13** in high yield together with small amounts of 5-benzoyl-2,4-diphenyloxazole (**18**). The structure of **13** was inferred



from its composition, spectral data, and chemical behavior. Specifically, the nmr spectrum ($CDCl_3$) exhibited a singlet at τ −3.01, a multiplet centered at τ 2.31, and a singlet at τ 3.63. The peak areas were in the ratio of 1:15:1. The fact that the chemical shift associated with the proton attached to the nitrogen was markedly deshielded and invariant with concentration strongly suggested that the benzamido group of **13** is *cis* to the benzoyl group. Chemical confirmation for this structure was obtained by hydrolysis of **13** to dibenzoylmethane. Comparison of the physical properties of **13** with those of the thermal product obtained from **1** revealed that the two compounds were basically different. The elucidation of the structure of the minor photoproduct as 5-benzoyl-2,4-diphenyloxazole (**18**) was based on its spectral properties, elemental composition, and an independent synthesis. Compound **18** could be prepared in high yield by the oxidation of **15** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in refluxing benzene.

The formation of **13** from **15** may be visualized as occurring by scission of the O–C bond followed by an unusual but not unprecedented 1,2-hydrogen shift.[16-18]



Having eliminated structures **5**, **8**, and **13** from further consideration, we feel that all of the evidence points strongly to 1,4-diphenyl-4-benzoyloxy-2-azabutadiene (**14**) as the structure of the thermal product of **1**. This assignment is supported by the spectral data, catalytic hydrogenation, and the reactivity of **14** toward sodium methoxide. The nmr spectrum of the thermal product showed multiplets at τ 1.72 (3 H) and 2.60 (14 H). The three-proton multiplet at τ 1.72 can be assigned to the *ortho* hydrogens of the imine phenyl ring and the imine hydrogen. The thermal product could be reduced with hydrogen and palladium on charcoal. The product isolated was identified as the

(11) H. W. Heine, M. E. Fetter, and E. M. Nicholsen, *J. Amer. Chem. Soc.*, **81**, 2202 (1959); H. W. Heine, W. G. Kenyon, and E. M. Johnson, *ibid.*, **83**, 2570 (1961); H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31**, 2662 (1966); H. W. Heine, *Agew. Chem., Int. Ed. Engl.*, **1**, 528 (1962).

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(13) F. E. Fanta and E. N. Walsh, *J. Org. Chem.*, **30**, 3574 (1965); **31**, 59 (1966).

(14) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 3828 (1965).

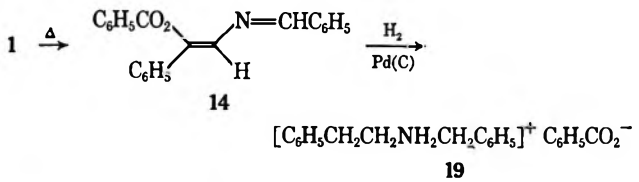
(15) P. Thyrum and A. R. Day, *J. Med. Chem.*, **8**, 107 (1965).

(16) G. W. Griffin, J. Covell, R. C. Petterson, R. M. Dodson, and G. Close, *J. Amer. Chem. Soc.*, **87**, 1410 (1965).

(17) D. I. Schuster and I. S. Krull, *ibid.*, **88**, 3456 (1966).

(18) A. Padwa, D. Crumrine, R. Hartman, and R. Layton, *ibid.*, **89**, 4435 (1967).

benzylphenethylammonium salt of benzoic acid (**19**) on the basis of its spectral data and by an independent synthesis of **19** from benzylphenethylamine and ben-



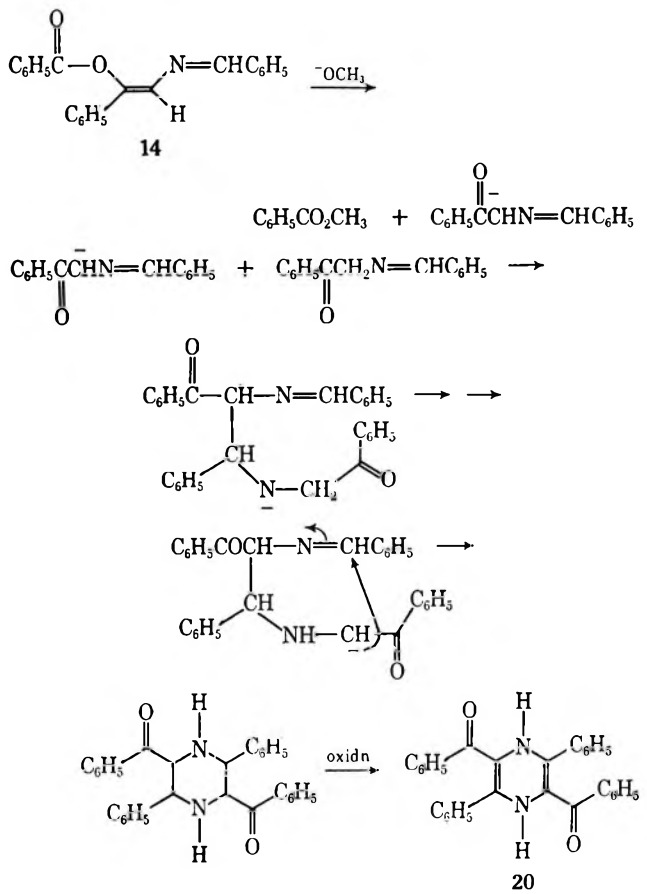
14

$[C_6H_5CH_2CH_2NH_2CH_2C_6H_5]^+ C_6H_5CO_2^-$

19

zoic acid. Treatment of **14** with sodium methoxide gave one major product that was assigned as 2,5-dibenzoyl-3,6-diphenyl-1,4-dihydropyrazine (**20**) on the basis of its analysis and spectral properties and from mechanistic considerations. A reasonable mechanism for the formation of **20** is presented in Scheme II.

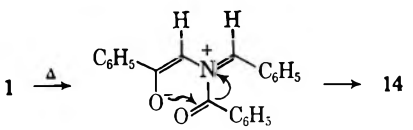
SCHEME II



20

In this postulated mechanism, sodium methoxide attacks the ester linkage to give a N-benzoylmethylbenzalimine anion which cyclizes to an intermediate hexahydropyrazine that in turn is air oxidized to the final product.

The mechanism by which **1** isomerizes to **14** and the intermediate or transition state involved in the reaction are of considerable interest. Recent work has demonstrated that appropriately substituted aziridines form adducts with various alkenes and alkynes when heated in inert solvents.[9,19-25] These reactions can be envisaged as occurring by an initial cleavage of the carbon–carbon bond of the aziridine ring to form a 1,3-dipole intermediate which subsequently adds to the unsaturated substrate. The mechanism that we propose for the above rearrangement (**1** → **14**) involves cleavage of the carbon–carbon bond of the aziridine ring to give a 1,3-dipole intermediate which subsequently rearranges to the final product by way of a benzoyl migration. Experiments designed to trap the 1,3-dipole intermediate by heating **1** in the presence of dimethylacetylene dicarboxylate, cyclohexene, or substituted butadienes were unsuccessful. The inability of an external trapping reagent to trap the 1,3-dipole intermediate suggests that either the isomerization is a concerted process or else the 1,3 dipole rearranges faster than it can be trapped. The thermal rearrangement of



dibenzoylaziridine **1** stands in marked contrast to previous work on related 1,3-diaroyl-2-arylaziridines.[10] The fact that a different route occurs in the thermal rearrangement of **1** to **14** suggests that either the nitro group plays an important role in the pyrolytic behavior of these small nitrogen heterocycles or else the structure of the rearranged product in the nitro system has been misassigned.

Experimental Section[26]

trans-**1,3-Dibenzoyl-2-phenylaziridine** (**1**).—To a mixture of 5.55 g (0.025 mol) of *trans*-2-phenyl-3-benzoylaziridine (**2**)[27] and 2.52 g (0.025 mol) of triethylamine in 100 ml of anhydrous benzene was added with stirring a solution of 3.50 g (0.025 mol) of benzoyl chloride in 75 ml of anhydrous ether. The mixture was stirred at room temperature for 2 hr and filtered; the precipitate that formed was washed well with water to dissolve the triethylamine hydrochloride. Careful low-temperature recrystallization from heptane–benzene gave 6.0 g of **1** as white needles, mp 127.5–129°.

The infrared spectrum (potassium bromide pellet) was characterized by bands at 5.95, 6.88, 7.06, 7.46, 8.10, 9.70, and 13.91 μ. The nmr spectrum in deuteriochloroform shows a multiplet centered at τ 2.40 (10 H), a doublet at 5.63 (1 H, J = 2.5 Hz), and a doublet at 5.92 (1 H, J = 2.5 Hz). The ultraviolet spectrum (95% ethanol) has maxima at 254 mμ (ϵ 23,500) and 316 (278).

Anal. Calcd for $C_{22}H_{17}O_2N$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.72; H, 5.22; N, 4.30.

Acid-Catalyzed Addition of Methanol to *trans*-1,3-Dibenzoyl-2-phenylaziridine.—A solution of 2.0 g of *trans*-1,3-dibenzoyl-2-phenylaziridine (**1**) in 50 ml of methanol containing 1 drop of concentrated hydrochloric acid was allowed to reflux for 1 hr. The mixture was concentrated *in vacuo*, and the crude residue

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(20) H. W. Heine, R. Peavy, and A. J. Durbetaki, *J. Org. Chem.*, **31**, 3924 (1966).
(21) A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965).
(22) A. Padwa and L. Hamilton, *J. Heterocycl. Chem.*, **4**, 118 (1967).
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(24) J. W. Lown, R. K. Smalley, and G. Dallas, *Chem. Commun.*, 1543 (1968).
(25) P. B. Woller and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 579 (1968).
(26) All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and Alfred Bernhardt Laboratories, Hohenweg, Germany. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 60 Mc with the Varian Associates high-resolution spectrophotometer. Tetramethylsilane was used as an internal standard.
(27) N. H. Cromwell, R. D. Babson, and C. A. Harris, *J. Amer. Chem. Soc.*, **65**, 312 (1943).

was cooled to give 2.1 g (95%) of a white solid. Recrystallization from methanol gave colorless needles, mp 158–159°. The structure of this material is assigned as 2-benzamido-1,3-diphenyl-3-methoxypropanone (3) on the basis of the following observations.

Anal. Calcd for $C_{23}H_{21}O_3N$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.51; H, 8.58; N, 3.89.

The infrared spectrum (potassium bromide pellet) shows strong absorptions at 3.05, 5.91, 6.09, 6.58, 6.91, 7.62, 8.21, 8.97, 12.53, 13.28, and 14.25 μ. The nmr spectrum ($CDCl_3$) is characterized by a multiplet centered at τ 2.49 (16 H), a doublet of doublets centered at τ 3.88 (1 H, J = 6 Hz, J = 6 Hz), a doublet at τ 5.28 (1 H, J = 6 Hz) and a singlet at τ 6.82 (3 H, OCH_3). The mass spectrum (70 eV) lacked a parent ion but exhibited prominent peaks at m/e (relative intensity) 327 (16, P − MeOH), 206 (12), 121 (25), 106 (33), 105 (100), 77 (43), 32 (19), and has metastable peaks at 56 and 130. The ultraviolet spectrum in 95% ethanol exhibited a maximum at 247 mμ (ϵ 18,650).

Acid-Catalyzed Addition of Ethanol to *trans*-1,3-Dibenzoyl-2-phenylaziridine.—A mixture of 2.0 g of *trans*-1,3-dibenzoyl-2-phenylaziridine (1) and 1 drop of concentrated hydrochloric acid in 50 ml of absolute ethanol was allowed to reflux for 1 hr. The mixture was concentrated *in vacuo* and the crude residue was cooled to give 1.1 g (92%) of white solid. Recrystallization from absolute ethanol gave colorless needles, mp 136–137°. The structure of this material is assigned as 2-benzamido-1,3-diphenyl-3-ethoxypropanone (4) on the basis of the following observations.

Anal. Calcd for $C_{24}H_{23}O_3N$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.16; H, 6.20; N, 3.79.

The infrared spectrum (potassium bromide pellet) exhibits bands at 3.01, 6.59, 6.75, 6.95, 7.33, 8.01, 9.10, 10.28, 12.88, 13.22, and 14.05 μ. The nmr spectrum ($CDCl_3$) shows a multiplet at τ 2.40 (16 H), a doublet of doublets at 3.83 (1 H, J = 7 Hz, J = 7 Hz), a doublet at 5.15 (1 H, J = 7 Hz), a complex multiplet centered at 6.68 (2 H) which contained a superimposed doublet of doublets (J = 7 Hz, J = 7 Hz) and a triplet at 9.04 (3 H, J = 7 Hz). The mass spectrum (70 eV) lacked a parent ion but has prominent peaks at m/e (relative intensity) 327 (14, P − EtOH), 135 (19), 106 (9), 105 (100), 77 (45), 45 (19), and has metastable peaks at 56, 84 and 130. The ultraviolet spectrum in 95% ethanol showed a maximum at 247 mμ (ϵ 14,000).

Treatment of 2-Benzamido-1,3-diphenyl-3-alkoxypropanones 3 and 4 with Base.—A mixture of 0.5 g of either 2-benzamido-1,3-diphenyl-3-methoxypropanone (3) or 2-benzamido-1,3-diphenyl-3-ethoxypropanone (4) and 30 ml of a freshly prepared 0.4 *N* sodium methoxide solution was stirred at 30° for 2 hr. The reaction mixture was diluted with water and extracted twice with benzene. The benzene extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* left a white solid which was recrystallized from methanol to give 0.4 g (96%) of colorless prisms, mp 138–139°. The structure of this compound was assigned as (α-benzamido)-*cis*-benzalacetophenone (5) on the basis of the following data.

Anal. Calcd for $C_{22}H_{17}O_2N$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.68; H, 5.28; N, 4.31.

The infrared spectrum (potassium bromide pellet) shows absorptions at 3.10, 6.09, 6.63, 6.78, 6.95, 7.58, 7.79, 7.97, 10.26, 10.77, 11.06, 12.21, 12.48, 12.68, 13.24 and 14.03 μ. The nmr spectrum ($CDCl_3$) was characterized by a multiplet at τ 2.43 (16 H), and a singlet at 3.36 (1 H). The mass spectrum (70 eV) indicated a molecular ion at m/e (relative intensity) 327 (9) and exhibited major peaks at 206 (8), 106 (9), 105 (100), 77 (45), 51 (8) and has metastable peaks at 56 and 130. The ultraviolet spectrum (in 95% ethanol) was characterized by maxima at 228 mμ (ϵ 22,320), 256 (18,460) and 294 (17,310).

Oxidation of (α-Benzamido)-*cis*-benzalacetophenone (5).—A sample of 0.6 g of (α-benzamido)-*cis*-benzalacetophenone (5) was dissolved in 8 ml of hot glacial acetic acid. To this solution was added 12 ml of a hot saturated solution of chromium trioxide in glacial acetic acid and the mixture was allowed to stir for 45 min. The dark green reaction mixture was poured onto ice-water and filtered. The residue was washed well with water and the solid was recrystallized from benzene–heptane to give white needles of N-phenylglyoxalbenzamide (6), mp 138–139°.

The infrared spectrum (potassium bromide pellet) showed strong bands at 5.80, 5.92, 6.10, 6.80, 7.44, 8.01, 8.22, 10.29, 10.99, 12.36, and 12.81 μ.

Structure 6 was confirmed by an alternate synthesis involving the oxidation of 2,5-diphenyloxazole.[6] To a sample of 0.5 g of 2,5-diphenyloxazole, dissolved in 7 ml of hot glacial acetic acid, was added 12 ml of a hot saturated solution of chromium trioxide in glacial acetic acid. After 5 min the reaction mixture was poured onto ice water and filtered to give a quantitative yield of N-phenylglyoxalbenzamide. Recrystallization from heptane–benzene gave 6 as white needles, mp 138–139°. The infrared spectrum was identical in all respects with that of 6 obtained from the oxidation of 5.

Acid Hydrolysis of *trans*-1,3-Dibenzoyl-2-phenylaziridine (1).—A mixture of 0.5 g of 1, 15 ml of dioxane, and 25 ml of a 10% hydrochloric acid solution was allowed to reflux for 10 hr. The reaction mixture was diluted with water and extracted twice with benzene. The combined benzene extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* left a crude white solid whose infrared spectrum indicated a mixture of benzoic acid and a new compound.

Fractional crystallization from benzene–heptane gave a white crystalline solid, mp 125–126°. The infrared spectrum of this material was identical in all respects with that of N-phenacylbenzamide (7). A mixture melting point of 7 with an authentic sample of N-phenacylbenzamide was undepressed.

Treatment of *trans*-1,3-Dibenzoyl-2-phenylaziridine (1) with Sodium Methoxide.—A solution of 0.1 g of 1 in 25 ml of freshly prepared 0.4 *N* sodium methoxide-methanol solution was allowed to stir at room temperature for 8 hr. The reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulfate, and the solvent removed *in vacuo* to give 0.09 g (94%) of a yellow-white solid. Recrystallization from methanol–water afforded colorless needles, mp 99.5–101°. The infrared spectrum of this material was identical in all respects with that of *trans*-2-phenyl-3-benzoylaziridine (2). A mixture melting point with authentic *trans*-2-phenyl-1-benzoylaziridine (2) was undepressed.

Thermal Isomerization of *trans*-1,3-Dibenzoyl-2-phenylaziridine (1).—A mixture of 1.0 g of 1 and 25 ml of benzene (or xylene) was allowed to reflux for 10 hr. Evaporation of the solvent *in vacuo* left a crude yellow solid which decomposed to a brown oil upon standing in air. Recrystallization of the crude yellow solid from heptane–benzene gave 0.85 g (85%) of light yellow prisms, mp 110–111°. Storage of this material in a moisture-free atmosphere prevented further decomposition. The structure of this material is assigned as 1,4-diphenyl-4-benzoyloxy-2-azabutadiene (14) on the basis of the following observations.

Anal. Calcd for $C_{22}H_{17}O_2N$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.47; H, 5.20; N, 4.16.

The infrared spectrum (potassium bromide pellet) is characterized by bands at 5.80, 6.10, 6.91, 8.11, 8.48, 9.22, 9.38, 9.74, 10.21, 12.96, and 13.27 μ. The nmr spectrum ($CDCl_3$) exhibits a complex multiplet at τ 1.72 (3 H) and a complex multiplet at 2.60 (14 H). The mass spectrum (70 eV) shows a molecular ion at m/e (relative intensity) 327 (35) and prominent peaks at 223 (10), 222 (55), 221 (10), 167 (18), 106 (19), 105 (100), 90 (14), 89 (13), 77 (72), and metastable peaks at 34, 50, 56, 126 and 151. The peak at m/e 167 corresponds to phenyltropylium which is presumably derived by fragmentation and rearrangement of the 222 peak (*i.e.*, loss of C=O and HCN). This is supported by the metastable at 126. The ultraviolet spectrum in absolute ethanol showed maxima at 230 mμ (ϵ 24,710) and 338 (28,670).

Heating a mixture of 0.5 g of 1, 1.0 g of dimethylacetylene dicarboxylate, and 25 ml of benzene gave only 14 and recovered acetylene.

Base-Catalyzed Ring Opening of *trans*-1,3-Dibenzoyl-2-phenylaziridine (1).—To a 0.6-g sample of 1 in 15 ml of glyme (distilled from lithium aluminum hydride) was added, under a nitrogen atmosphere, 0.9 g of sodium hydride (60% in mineral oil.)[28] The mixture was allowed to stir for 4 hr at room temperature during which time the color changed from pale yellow to orange-red. The insoluble material formed was filtered and the mother liquor was diluted with water and extracted with benzene. The benzene extracts were dried over anhydrous magnesium sulfate and removal of the solvent *in vacuo* left a white solid. Recrystallization from benzene–heptane gave white needles,

(28) Similar results were obtained when anhydrous potassium *t*-butoxide was used as the base.

mp 162.5–163°. The structure of this material is assigned as (α-benzamido)-*trans*-benzalacetophenone (**8**) on the basis of the following observations.

Anal. Calcd for $C_{22}H_{17}O_2N$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.50; H, 5.34; N, 4.24.

The infrared spectrum (potassium bromide pellet) is characterized by bands at 3.01, 6.06, 6.62, 6.78, 7.32, 7.89, 8.22, 10.27, 11.02, 11.57, 11.80, 12.48, 13.20, 13.64, and 14.06 μ. The nmr spectrum ($CDCl_3$) is characterized by a complex multiplet at τ 2.53 which contained a sharp singlet at 2.97. The mass spectrum (70 eV) had a molecular ion at *m/e* (relative intensity) 327 (19) and other major peaks at 222 (8), 206 (10), 106 (10), 105 (100), 78 (10), 77 (44), 51 (8), 40 (9), and metastable peaks at 56 and 130. The ultraviolet spectrum in 95% ethanol exhibited maxima at 233 mμ (ε 17,900), 257 (20,020), and 280 (16,820).

Oxidation of (α-Benzamido)-*trans*-benzalacetophenone (8).—A sample of 0.5 g of (α-benzamido)-*trans*-benzalacetophenone (**8**) was dissolved in 7 ml of hot glacial acetic acid and 10 ml of a hot saturated solution of glacial acetic acid was added. The combined solution was allowed to stir for 30 min. The dark green reaction mixture was then poured onto ice water and filtered. The residue was washed well with water and recrystallized from heptane–benzene to give white needles, mp 138–139°. This material was identified as N-phenylglyoxalbenzamide (**6**) by comparison of its infrared spectrum with that of authentic **6**. A mixture melting point of this material with an authentic sample of N-phenylglyoxalbenzamide **6** was undepressed at 138–139°.

Iodide Ion Catalyzed Isomerization of *trans*-1,3-Dibenzoyl-2-phenylaziridine (1).—A mixture of 2 g of **1** and 3 g of anhydrous sodium iodide in 50 ml of acetone was allowed to reflux for 3 hr. The solvent was removed *in vacuo* and the residue taken up in benzene. The benzene layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* afforded 1.95 g (97%) of a white solid which was recrystallized from methanol to give white needles, mp 82.5–84°. The structure of this material is assigned as *trans*-2,4-diphenyl-5-benzoyl-2-oxazoline (**15**) on the basis of the following observations.

Anal. Calcd for $C_{22}H_{17}O_2N$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.70; H, 5.31; N, 4.24.

The infrared spectrum of this material (potassium bromide pellet) is characterized by bands at 5.91, 6.06, 6.89, 7.44, 8.03, 9.37, 10.26, 11.98, 12.74, and 12.97 μ. The nmr spectrum (CCl_4) shows a complex multiplet at τ 2.41 (15 H) and an AB quartet at 6.38 (2 H, J = 6.5 Hz). The ultraviolet spectrum (pentane) is characterized by a maximum at 240 mμ (ε 22,100).

Irradiation of *trans*-2,4-Diphenyl-5-benzoyl-2-oxazoline (15) in Benzene.—A solution of 1.0 g of *trans*-2,4-diphenyl-5-benzoyl-2-oxazoline (**15**) of 1 l. of pentane was irradiated with an internal water-cooled mercury arc lamp (Hanovia Type L, 450 W) with a Pyrex filter to eliminate wavelengths below 280 mμ. Purified nitrogen was passed through the solution for at least 45 min before irradiation commenced, and a positive pressure of nitrogen was maintained throughout. Aliquots were withdrawn and analyzed by tlc. After 4 hr, the spot on a thin layer plate due to **15** has almost disappeared and two new spots had appeared in its place. Concentration of the solution *in vacuo* left a mixture of two compounds which could be separated by preparative thick layer chromatography.[29] The two products were identified as (β-benzamido)-*trans*-benzalacetophenone (**13**) and 5-benzoyl-2,4-diphenyloxazole (**18**).

Recrystallization of **13** from benzene heptane afforded 0.9 g (90%) of pale yellow prisms, mp 117–118°. The structure of this material is assigned as (β-benzamido)-*trans*-benzalacetophenone (**13**) on the basis of the following observations.

Anal. Calcd for $C_{22}H_{17}O_2N$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.41; H, 5.28; N, 4.07.

The infrared spectrum of this material in a potassium bromide pellet shows bands at 5.91, 6.15, 6.30, 6.40, 6.70, 6.85, 7.59, 7.68, 7.75, 8.03, 8.16, 8.79, 9.56, 9.78, 10.93, and 13.89 μ. The nmr spectrum ($CDCl_3$) shows a broad singlet at τ − 3.01 (1 H), a complex multiplet at 2.31 (15 H), and a singlet at 3.63 (1 H). The mass spectrum (70 eV) indicated a molecular ion at 3.63 (1 H). The mass spectrum (70 eV) indicated a molecular ion at *m/e* (relative intensity) 327 (2) and prominent peaks at 223 (20), 222 (100), 105 (56), 77 (47), 51 (8) and a metastable peak at 56. The ultraviolet spectrum in 95% ethanol was characterized by maxima at 257 mμ (ε 18,600) and 341 (22,760).

Structure **13** was further confirmed by the following chemical degradation. A mixture of 0.5 g of **13**, 15 ml of dioxane, and 15 ml of a 10% hydrochloric acid solution was allowed to reflux for 8 hr. The reaction mixture was diluted with water and extracted with benzene. The benzene layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded a crude solid. Recrystallization from heptane–benzene gave pale yellow prisms, mp 76–77°. The infrared spectrum of this material was identical in all respects with that of dibenzoylmethane. A mixture melting point of this material with authentic dibenzoylmethane was undepressed at 76–77°.

Recrystallization of **18** from benzene–heptane gave white needles, mp 139.5–140.5°. The structure of this material was assigned as 5-benzoyl-2,4-diphenyloxazole (**18**) on the basis of the following observations.

Anal. Calcd for $C_{22}H_{15}O_2N$: C, 81.21; H, 4.65; N, 4.31. Found: C, 81.12; H, 4.69; N, 4.21.

The infrared spectrum of this material in a potassium bromide pellet was characterized by bands at 6.06, 6.54, 7.37, 8.12, 8.61, 11.77, 12.76 and 13.96 μ. The nmr spectrum ($CDCl_3$) showed only a multiplet centered at τ 2.09. The mass spectrum (70 eV) exhibited a molecular ion at *m/e* (relative intensity) 325 (98) and prominent peaks at 39 (11), 51 (15), 63 (25), 77 (43), 89 (100), 105 (19), 117 (10), 165 (9), 192 (77), and 193 (14). The ultraviolet spectrum exhibited maxima at 265 mμ (ε 27,340) and 328 (13,620).

Structure **18** was further confirmed by an alternate synthesis from *trans*-2,4-diphenyl-5-benzoyl-2-oxazoline (**15**). A mixture of 0.20 g (0.0006 mol) of oxazoline **15** and 0.14 g (0.006 mol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 15 ml of benzene was allowed to reflux for 3 hr. A brown solid precipitated out as the reaction proceeded. The reaction mixture was then filtered and the filtrate concentrated *in vacuo* to give a dark oil. Preparative thick layer chromatography of the mixture produced only a single component which was recrystallized from benzene–heptane to afford white needles, mp 139.5–140.5°. The infrared spectrum of this material was identical in all respects with that of a sample of **18** obtained from the photolysis. A mixture melting point of the two samples was undepressed at 140°.

Acid Hydrolysis of *trans*-2,4-Diphenyl-5-benzoyl-2-oxazoline (15).—A mixture of 0.5 g of *trans*-2,4-diphenyl-5-benzoyl-2-oxazoline (**15**), 10 ml of 95% ethanol, and 10 ml of water was allowed to reflux for 18 hr. The reaction mixture was diluted with water and extracted with benzene. The benzene layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a yellow oil which was crystallized from chloroform–heptane to give 0.5 g (90%) of white needles, mp 138.5–140°. The structure of this product is assigned as N-1-phenyl-2-hydroxy-2-benzoylethylbenzamide (**16**) on the basis of the following observations.

Anal. Calcd for $C_{22}H_{19}O_3N$: C, 76.50; H, 5.55; N, 4.06. Found: C, 76.29; H, 5.56; N, 4.04.

The infrared spectrum of this material (potassium bromide pellet) was characterized by bands at 3.01, 5.92, 6.07, 6.58, 6.72, 7.11, 7.60, 7.80, 7.95, 9.01, 10.15, 13.14, 13.76, and 14.32 μ. The ultraviolet spectrum in 95% ethanol showed a maximum at 236 mμ (ε 17,620). The nmr spectrum ($CDCl_3$) was characterized by a multiplet centered at τ 2.41 (15 H), a doublet at 3.0 (1 H, J = 9 Hz, NH), a doublet of doublets at 4.28 (1 H, J = 9 Hz, J = 1.8 Hz, CHNH), a poorly resolved doublet of doublets at 4.52 (1 H, J = 4, J = 1.8 Hz, CHOH) and a poorly resolved doublet at 5.64 (1 H, J = 4 Hz, OH). Addition of deuterium oxide to the nmr tube simplified the spectrum and gave a multiplet at 2.41 (15 H), a doublet at 2.94 (1 H, J = 9 Hz, NH), a doublet of doublets at 4.28 (1 H, J = 9 Hz, J = 1.8 Hz, CHNH) and a sharp doublet at 4.52 (1 H, J = 1.8 Hz, CHOD). In order to complete the deuterium exchange, a sample of 0.1 g of **16** was dissolved in 10 ml of methanol–OD containing 1 drop of deuterium chloride (20% in D_2O). The solution was heated to reflux for 1 hr. The solvent was then removed *in vacuo* leaving a white solid whose nmr spectrum contained a multiplet at τ 2.41 (15 H) and an AB quartet at 4.39 (2 H, J = 1.8 Hz, DOCHCHND).

Oxidation of N-1-Phenyl-2-hydroxy-2-benzoylethylbenzamide (16).—A solution of 0.3 g of N-1-phenyl-2-hydroxy-2-benzoyl-

(29) Thick layer plates were prepared by spreading a slurry of 150 g of Merck $PF_{254+256}$ silica gel and 350 ml of distilled water onto 10 × 20 cm glass plates to an average thickness of 1.5 cm. The plates were allowed to dry at room temperature for 24 hr prior to use.

ethylbenzamide (16) in 5 ml of glacial acetic acid containing 10 ml of a hot saturated solution of chromium trioxide in glacial acetic acid was allowed to stir for 10 min. The dark green reaction mixture was poured onto ice water and filtered. The residue was washed with water and recrystallized from methanol to give a quantitative yield of dibenzamide as white needles, mp 144–145° (lit.[30] 144°). This material was identified as dibenzamide by a comparison of its infrared spectrum with that of an authentic sample prepared by the method of Lamberton and Standage.[30] A mixture melting point of these two materials was undepressed at 144–145°.

If the oxidation was allowed to proceed for only 2 min a partial oxidation product (17) as well as dibenzamide could be isolated by preparative thick layer chromatography. The structure of this material is assigned as N-1-phenyl-1-phenylglyoxylmethylbenzamide (17), mp 170–171°, on the basis of the following observations.

The infrared spectrum (in a potassium bromide pellet) was characterized by absorptions at 3.02, 5.84, 5.96, 6.06, 6.53, 6.89, 7.48, 7.71, 9.95, 11.82, 12.45, 13.20, 14.06, and 14.50 μ. The mass spectrum (70 eV) exhibited a molecular ion at m/e 343, prominent peaks at 222 (3.0), 221 (16.0), 165 (2.0), 106 (9.0), 105 (100), 52 (2.0), 51 (14.0), 50 (4.0), and had metastable peaks at 56 and 142.

Catalytic Hydrogenation of 1,4-Diphenyl-4-benzoyloxy-2-aza-butadiene (14).—A mixture of 0.08 g of 14 in 200 ml of dry methanol was hydrogenated in a Parr shaker over 0.1 g of 10% palladium on carbon at 50 psig for 3 hr. The catalyst was then removed by filtration and the filtrate concentrated *in vacuo* to leave a white solid, mp 206–208°. The structure of this compound was assigned as the benzylphenethylammonium salt of benzoic acid (19) on the basis of the following observations.

The infrared spectrum of 19 in a potassium bromide pellet showed broad adsorptions at 3.0 to 4.2, 6.3, 6.5, and 7.25 μ all of which are characteristic of benzoic acid salts. Additional bands appeared at 9.4, 9.8, 11.9, 13.3, 13.9, and 14.2 μ.

The structure of 19 was confirmed by generation of benzylphenethylamine from 19. A 0.05-g sample of 19 was dissolved in a 10% sodium carbonate solution and extracted with ether. The ether extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave an oil which was identical in all respects with an authentic sample of benzylphenethylamine.

Alternatively, treatment of 0.1 g of benzylphenethylamine with 0.1 g of benzoic acid in 3 ml of ether afforded a white precipitate. This material, mp 206–208°, was identical in all respects with the material isolated from the catalytic hydrogenation.

Treatment of 1,4-Diphenyl-4-benzoyloxy-2-aza-butadiene (14) with Sodium Methoxide.—A mixture of 0.3 g of 6 was dissolved in 20 ml of a freshly prepared 0.4 *N* sodium methoxide–methanol solution and was allowed to stir at room temperature for 4 hr. The colored reaction mixture was diluted with water and extracted twice with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded a crude bright yellow solid. Recrystallization from benzene–pentane produced yellow needles, mp 235–237° dec. The structure of this material was assigned as 2,5-dibenzoyl-3,6-diphenyl-1,4-dihydropyrazine (20) on the basis of the following observations.

Anal. Calcd for $C_{30}H_{22}O_2N_2$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.79; H, 5.23; N, 6.08.

The infrared spectrum (potassium bromide pellet) was characterized by bands at 3.09, 6.26, 7.06, 7.69, 8.05, 10.93, 11.31, 12.90, 13.47, and 14.25 μ. In order to demonstrate that the band at 3.09 was due to an N–H stretching mode, 0.01 g of 20 was allowed to reflux in methanol-OD for 1 hr. The solvent was removed *in vacuo* and the infrared spectrum revealed that the band at 3.09 μ (N–H) had disappeared and that a new band at 4.08 μ (N–D) had appeared. The nmr spectrum was characterized by a complex multiplet centered at τ 2.42. The mass spectrum (70 eV) had a molecular ion at m/e (relative intensity) 442 (3) and prominent peaks at 41 (37), 43 (62), 44 (40), 55 (38), 56 (16), 57 (80), 69 (30), 71 (50), 77 (68), 85 (33), 105 (100), 323 (35), 338 (40), 349 (30), 426 (60), 427 (20), and 428 (12). The ultraviolet spectrum in cyclohexane exhibited maxima at 235 mμ (ϵ 9100), 259 (6000), and 366 (5450).

(30) A. H. Lamberton and A. E. Standage, *J. Chem. Soc.*, **25**, (1960).

Registry No.—1, 24290-58-2; 3, 24807-13-4; 4, 24807-14-5; 5, 24806-70-0; 6, 24807-15-6; 8, 24806-71-7; 13, 23112-19-8; 14, 24294-71-1; 15, 24806-73-3; 16, 24807-17-8; 17, 24807-18-9; 18, 24807-19-0; 19 benzylphenethylammonium salt, 24807-20-3; 20, 24807-21-4.

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Pyridazines. XXXV. Oxidation Products of Some Simple and Bicyclic Pyridazines

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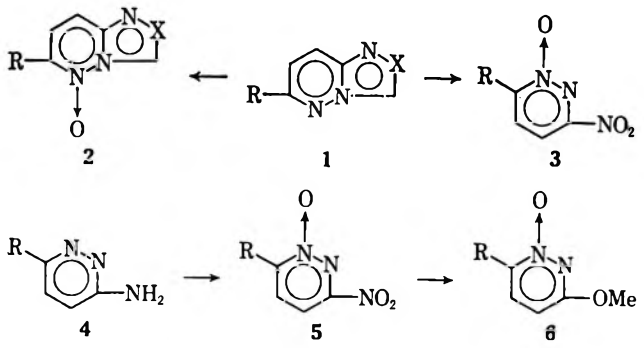
N-Oxides of imidazo[1,2-*b*]pyridazine and s-triazolo[4,3-*b*]pyridazine have been obtained by direct oxidation with concentrated hydrogen peroxide in polyphosphoric acid. With several bicyclic compounds further oxidation afforded pyridazine derivatives. 6-Amino bicyclic compounds were resistant toward N-oxidation but afforded the corresponding 6-nitro compounds. Several displacement reactions on substituted pyridazine N-oxides have been performed, and it was also shown that nmr spectral characteristics can be used for distinguishing the site of N-oxidation.

We recently reported[1] the first representative of azoloazine N-oxides with bridgehead nitrogen, *i.e.*, s-triazolo[4,3-*b*]pyridazine 5-oxides, which were synthesized by cyclization of the appropriate pyridazine N-oxides since previous direct N-oxidation procedures have failed. We now report the successful direct N-oxidation of such bicyclic systems with concentrated hydrogen peroxide in polyphosphoric acid.

Imidazo[1,2-*b*]pyridazine and 85% hydrogen peroxide in polyphosphoric acid below 40° afforded the 5-oxide (2, X = CH; R = H) in moderate yield. However, with a large excess of the oxidizing agent 3-nitropyridazine 1-oxide was formed by degradative oxidation. A greater tendency toward degradation compared with N-oxidation could be observed with 6-chloro- or 6-methoxyimidazo[1,2-*b*]pyridazine which were transformed into 6-chloro-3-nitropyridazine 1-oxide and 6-methoxy-3-nitropyridazine, respectively. In the last case, the possible alternative structure of the product as a methoxynitrosopyridazine N-oxide could

(1) A. Pollak, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, **5**, 513 (1968).



be excluded by the mass spectrum which showed peaks due to M − 30 (NO) and M − 46 (NO_2) loss, a pattern characteristic for organic nitro compounds.[2,3] So far, any variation of the composition of the oxidizing agent, *i.e.*, by employing 85% hydrogen peroxide in acetic, formic, or trifluoroacetic acid, left imidazo[1,2-*b*]-pyridazine unchanged and even traces of the expected 5-oxide could not be detected.

In a similar manner *s*-triazolo[4,3-*b*]pyridazine was oxidized into its 5-oxide (**2**, X = N; R = H) in low yield, a considerable amount of the starting bicyclic compound (**1**, X = N; R = H) remaining unchanged. Resistance toward N-oxidation was observed with 6-amino-*s*-triazolo[4,3-*b*]pyridazine and 6-aminoimidazo-[1,2-*b*]pyridazine, both of which afforded in good yield only the corresponding 6-nitro compounds (**1**, R = NO_2; X = CH or N). It appears that this amino-nitro group transformation greatly decreases the tendency toward N-oxidation and degradative oxidation, an effect undoubtedly due to the electron-withdrawing 6-nitro group.

Application of both polyphosphoric acid and highly concentrated hydrogen peroxide for N-oxidation of these azolopyridazines seems to be responsible for the successful progress of the reaction. Since the basicity of the attacked ring nitrogen is relatively low as judged from the calculated electron densities,[4] this would require a very reactive attacking species. The presence of polyphosphoric acid seems to be important for the uptake of the formed water, rather than acting as a proton donor or Lewis acid.

Since the above experience with the oxidative transformation of an amino group into nitro group could be of synthetic importance for the preparation of not readily accessible 3-nitropyridazine 1-oxides, experiments were extended in this direction.

In this manner 3-aminopyridazine afforded 3-nitropyridazine 1-oxide, and 3-amino-6-chloropyridazine was converted into 6-chloro-3-nitropyridazine 1-oxide. It is well known that 3-amino-6-chloropyridazine can be oxidized with hydrogen peroxide in acetic acid, however, to afford 6-amino-3-chloropyridazine 1-oxide.[5,6] Likewise, other 6-amino-3-substituted pyridazines are transformed into their mono-N-oxides, reaction taking place at the ring nitrogen adjacent to the carbon bearing the amino group[6] and the amino group being left intact in all cases. On the other hand, Koelsch and Gumprecht,[7] who obtained pyridazine N-oxide after treating pyridazine with 30% hydrogen peroxide in acetic acid at room temperature, were not able to nitrate this N-oxide. This was later effected by Itai and Natsume[8] under quite drastic reaction conditions; yet 4-nitropyridazine 1-oxide was formed.

Several displacement reactions have been performed on 6-chloro-3-nitropyridazine 1-oxide (**3**, R = Cl) which reacted with acetyl bromide to give the 6-bromo derivative (**5**, R = Br). Evidently, the displacement of the nitro group common to 3-nitropyridazine 1-oxide[9] and other nitropyridazine N-oxides,[10] under the action of acetyl chloride to give the corresponding chloro compounds, did not take place.

Also, in other nucleophilic displacement reactions the 6-chlorine atom of **3** (R = Cl) was replaced, except when it reacted with sodium methoxide to give 6-chloro-3-methoxypyridazine 1-oxide (**6**, R = Cl). This parallels the reaction of 3,6-dichloropyridazine 1-oxide with alkoxides where 3-alkoxy derivatives are the preponderant products.[10] Other nucleophiles similarly attack preferentially position 3 in 3,6-dichloropyridazine 1-oxide,[11,12] and the position reactivity in halopyridazine 1-oxides, based on kinetic measurements, follows the order 5 > 3 > 6 > 4.[13] Moreover, it has been concluded that the combined effect of a *meta* N-oxide group and an *ortho* nitrogen should be greater than the effect of an *ortho* N-oxide and *meta* nitrogen.

It appears that the above procedure of preparing 6-chloro-3-methoxypyridazine 1-oxide is advantageous of direct oxidation of 6-chloro-3-methoxypyridazine with hydrogen peroxide in acetic acid because, in the last-mentioned reaction, besides the expected N-oxide, also 6-chloro-3(2H)-pyridazinone and 6-methoxy-3-(2H)-pyridazinone are formed.[12,14] Pyridazine itself gave similarly in polyphosphoric acid its N-oxide, free from its 1,2-dioxide which could be obtained in low yield when using 50% hydrogen peroxide in acetic acid.[15]

6-Hydrazino-3-nitropyridazine 1-oxide was converted into the corresponding 6-azido compound **5**, (R = N_3) which, as anticipated, existed completely in the azido form. The destabilization of the otherwise fused tetrazole ring is similar to that of 3-azidopyridazine 1-oxide,[16,17] and the phenomenon of azidotetrazolo valence isomerization associated with fused tetrazolopyridazines has been discussed recently.[17,18]

There are some prominent features of nmr spectra of imidazo[1,2-*b*]pyridazine 5-oxide and *s*-triazolo[4,3-*b*]-pyridazine 5-oxide. Of particular significance is the signal for H_6, being in both cases sharp *vis-à-vis* to the same signal of the parent bicyclic compounds.

(2) G. Spiteller, "Massenspektrometrische Strukturanalyse organischer Verbindugen," Verlag Chemie, Weinheim, 1966, pp 143, 165.
(3) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 512.
(4) M. Japelj, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, **6**, 559 (1969).
(5) T. Horie, *Yakugaku Zasshi*, **82**, 627 (1962).
(6) T. Horie and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 114 (1963).
(7) C. F. Koelsch and W. H. Gumprecht, *J. Org. Chem.*, **23**, 1603 (1958).
(8) T. Itai and S. Natsume, *Chem. Pharm. Bull.* (Tokyo), **11**, 83 (1963).
(9) T. Itai and S. Natsume, *ibid.*, **11**, 342 (1963).
(10) M. Tišler and B. Stanovnik, *Advan. Heterocycl. Chem.*, **9**, 211 (1968).
(11) S. Sako, *Chem. Pharm. Bull.* (Tokyo), **10**, 956 (1962).
(12) T. Nakagome, *Yakugaku Zasshi*, **82**, 244 (1962).
(13) S. Sako and T. Itai, *Chem. Pharm. Bull.* (Tokyo), **14**, 269 (1966).
(14) T. Itai and S. Sako, *ibid.*, **10**, 989 (1962).
(15) I. Suzuki, M. Nakadate, and S. Sueyoshi, *Tetrahedron Lett.*, 1855 (1968).
(16) T. Itai and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **11**, 348 (1963).
(17) B. Stanovnik, M. Tišler, M. Ceglar, and V. Bah, *J. Org. Chem.*, **35**, 1138 (1970).
(18) B. Stanovnik and M. Tišler, *Tetrahedron*, **25**, 3313 (1969).

Here, the signal for H_6 is broad owing to the electric quadrupole moment of the neighboring nitrogen. This observation can be of diagnostic value in connection with the assignment of the N-oxidation site.

The same phenomenon is observed also with simple pyridazines. Here, because of the unsymmetrical structure with respect to the position of the N-oxide group, two positional isomers can exist. Application of nmr spectroscopy for determination of the position of N–O group in pyridazine N-oxides was based mainly on the position of chemical shifts. Thus, it was established that the signal of a proton attached to the carbon atom adjacent to the N-oxide group appears at a higher field than that of the proton attached to the carbon atom adjacent to the ring nitrogen.[19] Now, a comparison of the shape of such signals with those of the deoxygenated pyridazine allows an assignment of the N-oxidation site.

Experimental Section

Melting points were determined on a Kofler micro hot stage and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as KBr disks and nmr spectra were recorded on a JEOL JNM-60HL spectrometer using tetramethylsilane as internal standard. All mass spectra were recorded at a resolution of approximately 1000 on a CEC 21-110C instrument using direct sample insertion into the ion source which was operating at temperature of 170°. The ionization voltage was 70 V and the emission current 100 μA. Throughout this paper polyphosphoric acid Fluka, containing 83% P_2O_5, was used.

Imidazo[1,2-*b*]pyridazine 5-Oxide (2, X = CH; R = H).—A solution of imidazo[1,2-*b*]pyridazine (4.8 g) in polyphosphoric acid (100 g) was prepared at 60° and then cooled to 30°. Under stirring, hydrogen peroxide (6.0 g of 85%) was added during 2 hr in such a manner that the temperature did not surpass 40°. After the addition was complete, the mixture was left to stand at room temperature and in the dark for 48 hr. Upon dilution with water (200 ml), neutralization with sodium carbonate to pH 6, and extraction with four portions of 50 ml of chloroform, the combined extracts were dried and evaporated *in vacuo*. The yellow residue (2.9 g, 54%) was recrystallized from ethyl acetate to afford colorless crystals: mp 175–176°; nmr ($CDCl_3$) τ 1.80 (dd, H_3), 2.34 (d, H_2), 2.18 (dd, H_6), 3.00 (dd, H_7), 2.42 (ddd, H_8) ($J_{2,3}$ = 0.6, $J_{6,7}$ = 5.7, $J_{7,8}$ = 10.0, $J_{6,8}$ = 0.45 $J_{3,8}$ = ~0.2 cps).

Anal. Calcd for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.37; N, 3.95; H, 31.24.

Oxidation of 6-Chloroimidazo[1,2-*b*]pyridazine.—A stirred solution of 6-chloroimidazo[1,2-*d*]pyridazine (3.0 g) in polyphosphoric acid (50 g) was treated with hydrogen peroxide (1.0 g of 85%), and the mixture was left to stand at room temperature for 48 hr. After dilution with water (70 ml) and neutralization with sodium bicarbonate to pH 5, the mixture was extracted with chloroform (four portions of 30 ml) and the combined extracts were dried and evaporated to dryness. A thin layer chromatographic examination on silica gel, using commercially available plates (DC-Fertigplatten Kieselgel F 254, Merck) and developing them with ethyl acetate, revealed that the product is a mixture of the starting compound (R_f = 0.6) and another nonfluorescent compound (R_f = 0.8). The crude product (100 mg) was separated on a larger scale by thin layer chromatography and there were obtained 13 mg of the compound with an R_f value of 0.8. Upon recrystallization from ethyl acetate there were obtained yellow needles of mp 164–165°. The compound was found to be identical by undepressed mixture melting point and identical ir spectrum with 6-chloro-3-nitropyridazine 1-oxide (3, R = Cl).

Anal. Calcd for $C_4H_2ClN_3O_2$: C, 27.39; H, 1.15; N, 23.96. Found: C, 27.49; H, 1.46; N, 24.18.

6-Nitroimidazo[1,2-*b*]pyridazine (1, X = CH; R = NO_2).—6-Aminoimidazo[1,2-*b*]pyridazine (2.0 g) was treated in the same manner as above with hydrogen peroxide (3.0 g of 85%) and using 50 g of polyphosphoric acid. After 24 hr crushed ice was added (50 g) to the reaction mixture which was then neutralized with $NaHCO_3$ to pH 5. The obtained product (1.8 g, 73%) was recrystallized from ethyl acetate, mp 145–146°.

Anal. Calcd for $C_6H_4N_4O_2$: C, 43.91; H, 2.46; N, 34.14. Found: C, 44.22; H, 2.62; N, 34.25.

In the mass spectrum, besides the peak for molecular ion (164) there is a peak of very low intensity at M − 30 (loss of NO) and an intense peak at M − 46 (loss of NO_2). Further fragmentation process involves loss of HCN (*m/e* 91 and 64).

6-Methoxy-3-nitropyridazine from 6-Methoxyimidazo[1,2-*b*]pyridazine.—The method to obtain 6-nitroimidazo[1,2-*b*]pyridazine was followed, starting with 6-methoxyimidazo[1,2-*b*]pyridazine (1.5 g). For analysis the crude product (1.1 g, 70%) was sublimed at 130° (0.01 mm), mp 143–144° (lit.[20] mp 142–143°).

Anal. Calcd for $C_5H_5N_3O_3$: C, 38.71; H, 3.25; N, 27.09. Found: C, 39.01; H, 3.59; H, 27.02.

3-Nitropyridazine 1-Oxide (3, R = H). A.—A solution of imidazo[1,2-*b*]pyridazine (1.2 g) in polyphosphoric acid (50 g) was treated with hydrogen peroxide (4.0 g of 85%) at such a rate as to keep the temperature of the reaction mixture between 35 and 40°. After addition was complete, the mixture was left to stand in the dark at room temperature for 24 hr, after which hydrogen peroxide (2.0 g) was added. After 48 hr at room temperature, water (60 ml) was added, and the mixture was neutralized with sodium carbonate and extracted with chloroform (four times with 30 ml). After the solvent was removed the residue (0.4 g, 29%) was crystallized from ethyl acetate to give yellow crystals with mp 164–165°. There was no depression in melting point on admixture with the product prepared as described in section B and ir spectra were identical.

B.—3-Aminopyridazine (1.9 g) was dissolved in polyphosphoric acid (50 g) at 100° and after the solution was cooled to 30°, under stirring, hydrogen peroxide (4.0 g of 85%) was added dropwise at such a rate as to keep the temperature in the range of 30–40° (about 3 hr). After 24 hr, water (50 ml) was added, the mixture neutralized with sodium carbonate to pH 6, and the yellow precipitate collected. Upon recrystallization from ethyl acetate yellow crystals (1.8 g, 65%) of mp 165–166° (lit.[9] mp 166°) were obtained. The compound was identical with the product prepared as described in section A. Nmr ($CDCl_3$)-τ 1.81 (d, H_4), 1.30 (dd, H_5), 1.86 (d, H_6) ($J_{4,5}$ = 6.0, $J_{5,6}$ = 1.3 cps, $J_{4,6}$ is not observed).

***s*-Triazolo[4,3-*b*]pyridazine 5-Oxide (2, X = N; R = H).**—A solution of *s*-triazolo[4,3-*b*]pyridazine (2.4 g) in polyphosphoric acid (60 g) was prepared at 100°, cooled to 30°, and, with stirring, treated at once with hydrogen peroxide (2.0 g of 85%). After 24 hr at room temperature, the mixture was treated again with the same quantity of hydrogen peroxide and left to stand for 48 hr. Thereafter, the reaction mixture was diluted with water (150 ml) and neutralized with sodium carbonate to pH 6. After extraction with chloroform (four portions of 40 ml) and evaporation of the solvent, there were obtained 1.3 g of the crude product. Thin layer chromatographic analysis, using commercially available plates (DC-Fertigplatten Kieselgel F 254, Merck, and ethyl acetate for developing), revealed that the product consisted of the unreacted starting compound and its N-oxide. The first compound was removed by sublimation *in vacuo* at 130° (0.01 mm) and the remaining N-oxide (0.5 g, 18%) was recrystallized from ethanol to give colorless crystals: mp 243–244°; a mixture melting point with an authentic specimen[1] showed no depression and ir spectra were identical; nmr ($CDCl_3$) τ 0.26 (d, H_3), 1.65 (d, H_6), 2.54 (dd, H_7), 1.96 (dd, H_8), ($J_{6,7}$ = 5.6, $J_{7,8}$ = 9.5; $J_{3,8}$ = 0.8, $J_{6,8}$ = ~0.1 cps).

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.25; H, 2.71; N, 41.30.

6-Nitro-*s*-triazolo[4,3-*b*]pyridazine (1, X = N; R = NO_2).—The procedure as described for the preparation of 6-nitroimidazo-[1,2-*b*]pyridazine was followed. There were employed 6-amino-*s*-triazolo[4,3-*b*]pyridazine (1.35 g), polyphosphoric acid (40 g), and hydrogen peroxide (2.0 g of 85%). After 24 hr the mixture was diluted with water (50 ml) and neutralized with sodium carbonate to pH 6; the product was filtered off, washed with water, and dried *in vacuo*. The crude product (1.1 g, 67%)

(19) K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 235 (1963).

(20) T. Nakagome, *Yakugaku Zasshi*, **81**, 554 (1961); *Chem. Abstr.*, **55**, 21134 (1961).

was (for analysis) recrystallized from ethanol to give yellow needles with mp 200–201°.

Anal. Calcd for $C_5H_3N_5O_2$: C, 36.37; H, 1.83; N, 42.42. Found: C, 36.15; H, 1.95; N, 42.25.

Pyridazine 1-Oxide.—A stirred solution of pyridazine (1.6 g) in polyphosphoric acid (40 g) and hydrogen peroxide (1.6 g, 85%) was added in one portion and the mixture was left to stand for 24 hr. After dilution with water (100 ml), neutralization with sodium carbonate, and extraction (four 30-ml portions of chloroform), the extracts were concentrated *in vacuo*. The crude product (1.6 g, 84%) was (for analysis) purified by distillation under high vacuum: mp 38–39° (lit.[7] mp 38–39°); nmr ($CDCl_3$) τ 1.70 (m, H_3), 3.00 (ddd, H_4), 2.43 (ddd, H_5), 1.92 (ddd, H_6) ($J_{4,5} = 7.5$, $J_{5,6} = 6.0$, $J_{4,6} = 1.0$, $J_{3,5} = 2.4$, $J_{3,6} = 0.6$ cps).

The crude product was examined by thin layer chromatography, but no traces of eventually present 1,2-dioxide could be detected.

6-Chloro-3-nitropyridazine 1-Oxide (3, R = Cl) was obtained from 3-amino-6-chloropyridazine (4.0 g) in essentially the same way as pyridazine 1-oxide with the exception that initial heating was necessary to dissolve the compound in polyphosphoric acid and then the solution was cooled to 35°. There were employed 6.0 g of 85% hydrogen peroxide and 50 g of polyphosphoric acid. The crude product was recrystallized from ethyl acetate to give yellow needles (3.0 g, 57%) with mp 164–165°.

Anal. Calcd for $C_4H_2ClN_3O_3$: C, 27.39; H, 1.15; N, 23.96. Found: C, 27.48; H, 1.45; N, 23.74.

6-Chloro-3-methoxypyridazine 1-Oxide (6, R = Cl).—Compound **3** (R = Cl; 1.75 g) and a solution of sodium methoxide (prepared from 0.25 g of sodium and 15 ml of absolute methanol) were left to stand at room temperature for 24 hr. The residue, obtained from concentration of the reaction mixture *in vacuo*, was crystallized twice from ethyl acetate to give colorless crystals, mp 160–162° (lit.[14] mp 159–161°).

Anal. Calcd for $C_5H_5ClN_2O_2$: C, 37.42; H, 3.14; N, 17.45. Found: C, 37.74; H, 3.01; N, 17.62.

6-Bromo-3-nitropyridazine 1-Oxide (5, R = Br).—A mixture of **3** (R = Cl, 0.5 g) and acetyl bromide (15 ml) was heated under reflux for 3 hr to obtain a solution. Excess of acetyl bromide was removed *in vacuo;* the residue was treated with ice (10 g) and neutralized with sodium bicarbonate. The crude product (0.4 g, 65%) was purified by recrystallization from ethyl acetate, mp 184–185°.

Anal. Calcd for $C_4H_2BrN_3O_3$: C, 21.85; H, 0.92; N, 19.11. Found: C, 22.25; H, 1.27; N, 18.92.

6-Anilino-3-nitropyridazine 1-Oxide (5, R = NHC_6H_5).—A suspension of 6-chloro-3-nitropyridazine 1-oxide (0.35 g) in ethanol (5 ml) and aniline (0.2 g) was heated under reflux for 3 hr. The obtained product was recrystallized from ethanol to give orange needles of mp 186–187° (yield 67%).

Anal. Calcd for $C_{10}H_8N_4O_3$: C, 51.72; H, 3.47; N, 24.13. Found: C, 51.77; H, 3.78; N, 23.86.

In essentially the same way **6-morpholino-3-nitropyridazine 1-oxide** was obtained in 64% yield, mp 214–215° (from ethanol).

Anal. Calcd for $C_8H_{10}N_4O_4$: C, 42.48; H, 4.46; N, 24.77. Found: C, 42.49; H, 4.73; N, 24.69.

6-Hydrazino-3-nitropyridazine 1-Oxide (5, R = $NHNH_2$).—A suspension of compound **3** (R = Cl, 1.75 g) in methanol (30 ml) was treated with hydrazine hydrate (1.0 g of 100%). The The resulting dark mixture was stirred at room temperature for 6 hr and the yellow needles which formed were filtered off and washed with methanol. Upon recrystallization from dilute methanol the pure compound melted at 187–188°.

Anal. Calcd for $C_4H_5N_5O_3$: C, 28.07; H, 2.95; N, 40.93. Found: C, 28.35; H, 2.55; N, 40.82.

The benzylidene derivative was prepared in the usual way and had mp 199–200°.

Anal. Calcd for $C_{11}H_9N_5O_3$: C, 50.96; H, 3.50; N, 27.02. Found: C, 51.11; H, 3.80; N, 27.06.

6-Azido-3-nitropyridazine 1-Oxide (5, R = N_3).—The above hydrazino compound (0.34 g) was dissolved in hydrochloric acid (5 ml of 5%) and the solution was cooled to 0°. Under stirring, a solution of sodium nitrite (0.14 g in 1 ml of water) was added dropwise and, after addition was complete, stirring was continued for 10 min. The separated product was recrystallized from ethyl acetate and, *n*-hexane to give (0.2 g, 55%) pale yellow plates of mp 119–120°, ir, in KBr, 2119 cm^{-1} (N_3).

Anal. Calcd for $C_4H_2N_6O_3$: C, 26.38; H, 1.11; N, 46.15. Found: C, 26.70; H, 1.36; N, 46.44.

Registry No.—**1** (X = CH; R = NO_2), 24716-49-2; **1** (X = N; R = NO_2), 24716-50-5; **2** (X = CH; R = H), 24716-51-6; **2** (X = N; R = H), 20552-65-2; **3** (R = Cl), 24716-53-8; **3** (R = H), 24716-54-9; **5** (R = Br), 24710-95-0; **5** (R = NHC_6H_5), 24704-30-1; **5** (R = $NHNH_2$), 24704-31-2; benzylidene derivative of **5** (R = $NHNH_2$), 24710-96-1; **5** (R = N_3), 24710-97-2; **6** (R = Cl), 14634-52-7; pyridazine 1-oxide, 1457-42-7; 6-morpholino-3-nitropyridazine 1-oxide, 24711-00-0.

Acknowledgment.—We wish to thank Dr. J. Marsel from Institute J. Stefan, Ljubljana, for recording some mass spectra.

Oxadiaziridines, the Cyclic Form of an Azoxy Group. Synthesis, Valence Isomerism, and Reactivity[1a,b]

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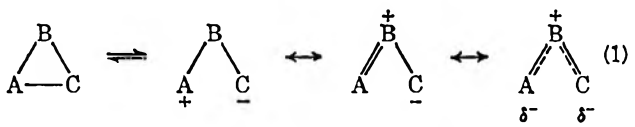
The photolysis of alkyl azoxy compounds RNN(O)R (**11a**, R = *t*-butyl; **11b**, R = *n*-butyl) in pentane affords a new three-membered-ring heterocycle, an oxadiaziridine (**12a**, R = *t*-butyl; **12b**, R = *n*-butyl). The oxadiaziridines revert to the azoxy compounds, $t_{1/2}$ at 28° ≃ 5 hr. The isomerization is catalyzed by acids (fivefold acceleration for **12a** by 1.7 *M* $Cl_2CHCOOH$ in CCl_4) and shows a slight solvent effect (k_{rel} for **12a** in CCl_4, CH_3OH, CH_3NO_2: 1, 2, 2.5). Compound **12a** is reduced to the corresponding azo compound by acidified NaI in acetone; it is generally unreactive toward $LiAlH_4$ or CH_3Li. Compounds **11b** and **12b** are reduced to the corresponding azo compound by $LiAlH_4$. Compound **12b** is reduced by CH_3Li to azobutane and butyraldehyde *n*-butylhydrazone; **11b** reacts with CH_3Li to afford 1-methylazobutane.

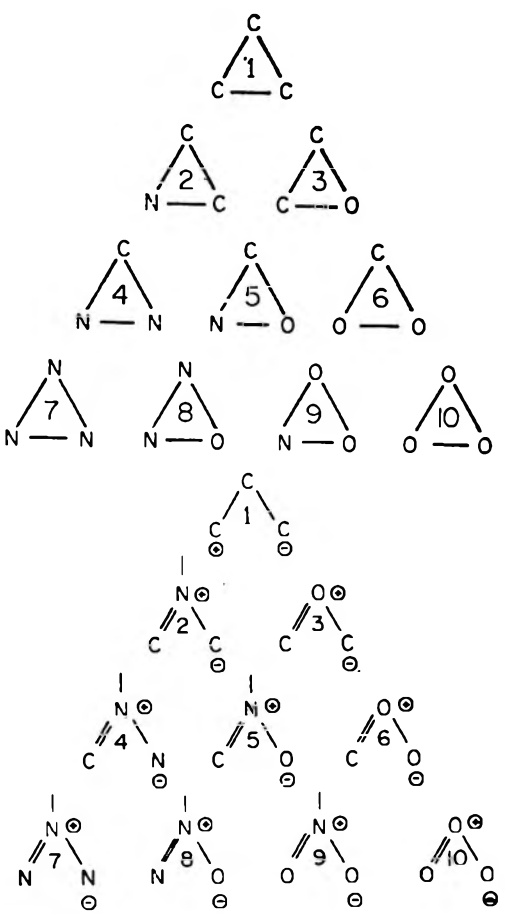
The interconversion of a three-membered ring with an open-chain dipolar form constitutes a type of valence isomerism that has received little attention (eq 1).



(1)

Scheme I illustrates all of the possible combinations for saturated three-membered rings containing carbon, nitrogen, and oxygen and a corresponding dipolar form.[2]

SCHEME I



Systems isolable in covalent form are **1**, **2**, **3**, **4**,[3a] and **5**.[3a,b] Those isolable in dipolar form are **5**,[3a,b] **8**, **9**, and **10**. There is some evidence for the transient existence of dipolar forms **2**,[3c] **3**,[3d] **4**,[3e,f] and **6**.[3g] The ability to exist in a dipolar form is obviously tied to the accommodations for the charges: to the availability of a lone pair on atom B, to the electronegativity of atoms A and C, and to the substituents attached to A and C (eq 1).[4] The relationship between the (isolable) covalent form and a transient dipolar form has been examined for **2**[3c] and **3**,[3d] and in the case of **2** the stereochemistry of the ring-opening reaction (conrotatory) has been established.[3c] For only one of the ten combinations—**5** in the center of the triangle—has it been possible to isolate both the covalent and the dipolar form[3b] for simple substituents.[5]

In recent years, the use of bulky substituents has resulted in the synthesis of small rings of enhanced stability (diaziridinones,[6a] aziridinones,[6b] cyclopropanones[7]). The stabilizing effect of tertiary alkyl substituents in these systems may be due to impeded attack at the carbonyl group, hindrance to concerted ring opening, or more subtle effects. These results encouraged the further examination of adequately hindered, new ring systems. We describe here the synthesis of the oxadiaziridine ring system **8**[8] and a number of reactions of this new class. Interestingly, bulky sub-

(1) (a) Supported in part by the National Science Foundation; (b) F. D. Greene and S. S. Hecht, *J. Amer. Chem. Soc.*, **89**, 6761 (1967); (c) National Institutes of Health Predoctoral Fellow, 1965–1968.

(2) The appropriate number of substituents is assumed to be attached to C, N, and O corresponding to the saturated valence states of these atoms.

(3) (a) E. Schmitz, "Dreiringe mit Zwei Heteroatomen," Springer-Verlag, New York, N. Y., 1967; (b) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957); (c) R. Huisgen, W. Scheer, and H. Huber, *ibid.*, **89**, 1753 (1967); (d) W. J. Linn, O. W. Webster, and R. E. Benson, *ibid.*, **87**, 3651 (1965); (e) R. Huisgen, *Proc. Chem. Soc.*, 357 (1961); (f) *Helv. Chim. Acta*, **50**, 2421 (1967); (g) R. Criegee, A. Kerckow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955); P. D. Bartlett and T. G. Traylor, *J. Amer. Chem. Soc.*, **84**, 3408 (1962); see also R. W. Murray, *Accounts Chem. Res.*, **1**, 313 (1968).

(4) The incorporation of the groups of Scheme I into aromatic systems leads to many additional examples: *e.g.*, (a) for dipolar form **3**, see E. F. Ullman and W. A. Henderson, Jr., *J. Amer. Chem. Soc.*, **88**, 4942 (1966); (b) for **4**, see J. Streith and J. M. Cassal, *Tetrahedron Lett.*, 4541 (1968); (c) for dipolar form **7**, see M. J. Perkins, *J. Chem. Soc.*, 3005 (1964); see also M. S. Gibson, *Nature*, **193**, 474 (1962).

(5) With rather specialized substituents,[4] both covalent and dipolar forms have been isolated, *e.g.*, for **3**, see ref 4a.

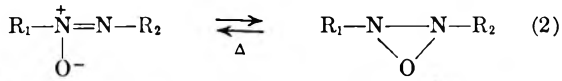
(6) (a) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969); (b) J. C. Sheehan and J. H. Beeson, *J. Amer. Chem. Soc.*, **89**, 362 (1967).

(7) J. F. Pazos and F. D. Greene, *ibid.*, **89**, 1030 (1967).

(8) The cyclic structure for **8** has appeared in the early literature as a formulation for the azoxy group. In recent times, a diaryloxadiaziridine has been proposed as an intermediate in the Wallach rearrangement of azoxybenzenes to hydroxyaryl azo compounds [M. M. Shemyakin, V. I. Maimind, and Ts. E. Agadzhanyan, *Chem. Ind.* (London) 1223 (1961)]. For further references on the Wallach rearrangement, see E. Buncel, A. Dolenko, I. G. Czizmadia, J. Pincock, and K. Yates, *Tetrahedron*, 6671 (1968), and C. S. Hahn, K. W. Lee, and H. H. Jaffé, *J. Amer. Chem. Soc.*, **89**, 4975 (1967).

stituents do not appear to be essential to the synthesis or stability of this system.

Synthesis of Oxadiaziridines.—Two methods have been examined: photolysis of azoxy compounds[9] and oxidation of azo compounds. Photolysis of azoxy compounds **11a–c** in pentane solution at 10–20° with a Hanovia Type L lamp resulted in ring closure to oxadiaziridines **12a–c.**



(2)

11a, $R_1 = R_2 = t$-butyl
b, $R_1 = R_2 = n$-butyl
c, R_1 = Me; $R_2 = t$-butyl

12a, $R_1 = R_2 = t$-butyl
b, $R_1 = R_2 = n$-butyl
c, R_1 = Me; $R_2 = t$-butyl

Assignment of structure **12** to the photoproducts is based on spectral data (see Table I), molecular weight,

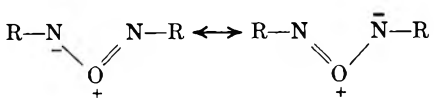
TABLE I

SPECTRAL PROPERTIES OF **11a,b** AND **12a,b**

	Nmr, ppm	Ir, cm^{-1}	Uv, $m\mu$ (ϵ)
11a	1.25 (9 H, s)	1495, s	221 (5535)
	1.46 (9 H, s)	1295	
12a	1.00 (18 H, s)		None
11b	4.17 (2 H, t)	1500	218 (8088)
	3.37 (2 H, t)	1315	
	2.0–0.8 (14 H, m)		
12b	2.63 (4 H, t)		None
	2.0–0.8 (14 H, m)		

volatility, and quantitative thermal isomerization back to the azoxy compounds. Oxadiaziridine **12c** was observed in the photolysis mixture but could not be isolated. Details are given in the Experimental Section.

A possible alternative structure, **13**, has not been rigorously excluded but is considered less likely than **12** on the basis of the lack of reactivity of photoproducts **a** and **b** toward 1,3 dipolarophiles and toward water, and the lack of uv absorption. Peracid oxidation of

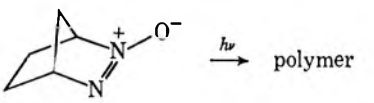


13

azo compounds is a known method for the synthesis of azoxy compounds. In view of the facile isomerization of oxadiaziridines to azoxy compounds (see section on reactivity) and the peracid oxidation of imines to oxaziridines,[3b] it seemed possible that low-temperature oxidation of azo compounds might first afford oxadiaziridines. Oxidation of azo-*t*-butane[10] with *m*-chloroperbenzoic acid or peracetic acid at 0° showed immediate appearance of azoxy infrared bands and provided no evidence for formation of the oxadiaziridine.

Both the azoxy compounds and the oxadiaziridines are capable, in theory, of existence in *cis* and *trans* forms. Steric considerations suggest the *trans* structure for **11a** and **12a**.[11,12] Nmr comparisons suggest that azoxy-*n*-butane (**11b**) has the *trans* structure. Di-*n*-butyloxadiaziridine could be either *cis* or *trans*. The nmr spectrum is suggestive of a single species. Interconversion of *cis*- and *trans*-*n*-butyloxidiaziridine (*e.g.*, by nitrogen inversion) would be expected to be slow by analogy to diaziridines[13] and oxaziridines.[13]

The photolysis of 2,3-diazabicyclo[2.2.1]-2-heptene N-oxide (**14**)[12] was studied in the hope of preparing a *cis*-substituted oxidiaziridine. Large amounts of uncharacterized polymeric material were obtained. No evidence was found for the presence of the oxadiaziridine.



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Reactivity of Oxadiaziridines.—Thermal isomerization of the oxadiaziridines to the azoxy compounds is facile, quantitative, and first order (Table II). Two

TABLE II

ISOMERIZATION OF OXADIAZIRIDINES TO AZOXYALKANES IN NEUTRAL AND ACIDIC MEDIA

	$t_{1/2}$, min (28°)	
Compd	CCl_4	CCl_4, 1.74 *M* in Cl_2CHCO_2H
12a	290	45
12b	270	70

aspects are of special interest. Firstly, the rates of isomerization for the *t*-butyl compound **12a** and the *n*-butyl compound **12b** are almost the same, implying that the bulky alkyl substituents convey no *special* stabilizing effect in this system. Secondly, the rate of isomerization of **12a** to **11a** is quite insensitive to the polarity of the medium[14] (relative rates: CCl_4, 1; CH_3OH, 2; CH_3NO_2, 2.5) implying that at the transition state of the ring-opening reaction one has not made much progress toward the charge distribution of the azoxy compound.

The stereochemistry of the ring-opening reaction is not known. The spectral properties of the azoxy-*n*-butane obtained from thermal isomerization of **12b** strongly suggest the presence of a single (the starting) isomer, presumably *trans*.

In the stronger acid medium of trifluoroacetic acid, di-*t*-butyloxadiaziridine is rapidly converted to *t*-butyl trifluoroacetate (78% yield). The same reaction is observed with azoxy-*t*-butane (92% yield of the tri-

(9) For the closely related photochemical conversion of nitrones to oxaziridines, see J. S. Splitter and M. Calvin, *J. Org. Chem.*, **30**, 3427 (1965). Photolysis of azoxymethane has been reported [B. G. Gowenlock, *Can. J. Chem.*, **42**, 1936 (1964)] giving C_2H_6, CH_4, N_2, and N_2O. Photolysis of aryl azoxy compounds has been reported to give *o*-hydroxyaryl azo compounds [G. M. Badger and R. G. Butley, *J. Chem. Soc.*, 2243 (1954)].

(10) "Azo-*t*-butane" is 1,1,1′,1′-tetramethylazoethane; "azoxy-*t*-butane" is 1,1,1′,1′-tetramethylazoxyethane.

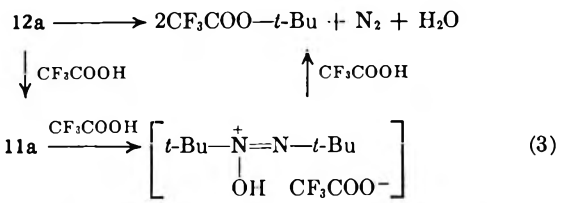
(11) We do not know of any *cis* acyclic aliphatic compounds. The compounds reported by B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **27**, 413 (1962), have been reassigned dimeric structures (C. E. Wintner, Ph.D. Thesis, Harvard University, 1963). Cyclic azoxy compounds are known (ref 12).

(12) F. D. Greene and S. S. Hecht, *Tetrahedron Lett.*, 575 (1969).

(13) A. Mannschreck and W. Seitz, *Angew. Chem. Int. Ed. Engl.*, **8**, 212 (1969).

(14) See S. Brownstein, *Can. J. Chem.*, **38**, 1590 (1960), and references cited therein; see also E. M. Kosower, "An Introduction to Physical-Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1968, Chapter 2.6–2.8.

fluoroacetate), possibly *via* a route such as that shown in eq 3. In this medium (CF_3COOH), di-*n*-butyloxa-

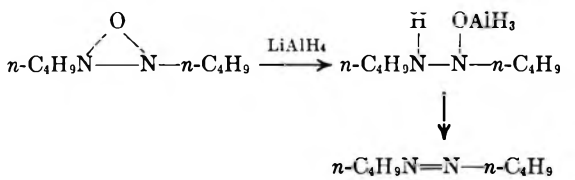


(3)

diaziridine is isomerized to azoxy compound. In contrast to azoxy-*t*-butane, azoxy-*n*-butane is unchanged by trifluoroacetic acid after 24 hr at room temperature.[15]

Reduction Reactions.—Di-*t*-butyloxadiaziridine is converted to azo-*t*-butane[10] (95%) by the action of acidified sodium iodide in acetone. This reaction can be used to assay samples of the oxadiaziridine. (However, spectral methods of assay are simpler.)

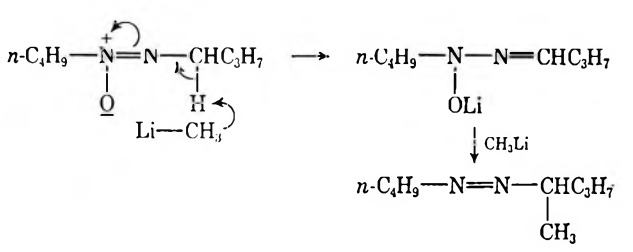
Di-*t*-butyloxadiaziridine is not reduced by lithium aluminum hydride in ether at room temperature. Di-*n*-butyloxadiaziridine is reduced to azobutane in 40% yield.



The same pattern is seen with lithium aluminum hydride and the azoxy compounds; the di-*t*-butyl derivative is recovered unchanged, while azoxy-*n*-butane is converted to azo-*n*-butane in 80% yield.

Reactions with Methyllithium.—The reaction of di-*t*-butyloxadiaziridine with methyllithium at room temperature proceeds sluggishly. Interruption of the reaction after 1 hr at room temperature gives a 7% yield of azo-*t*-butane,[10] while the remainder of the material is oxadiaziridine and azoxy-*t*-butane[10] (resulting from isomerization). Azoxy-*t*-butane, when treated under the same conditions, is slowly reduced to the azo compound (9% after 18 hr at 25°).

When azoxy-*n*-butane is mixed at 0° with a solution of methyllithium, a vigorous reaction takes place with evolution of gas and development of an orange color. Quenching results in decolorization and the isolation of 1-methyl-azobutane (**15**) in 30% yield as the single major product. The presence of the corresponding C_9 hydrazones is also indicated (see Experimental Section). The reaction of di-*n*-butyloxadiaziridine with



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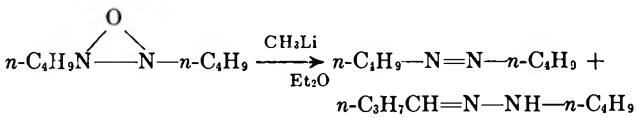
methyllithium follows a different course. In this case, the major products are found to be azo-*n*-butane (50%) and butyraldehyde *n*-butylhydrazone (25%). The



hydrazone may arise by isomerization of azo-*n*-butane or by extraction of an α hydrogen at an intermediate stage.

A number of conditions which gave no reaction with the oxadiaziridines and the azoxy compounds are summarized in the Experimental Section.

Experimental Section

Azo-*n*-butane.[16]—An aqueous solution of sodium hypochlorite (80 ml, 1.5 *M*) was added at 0° with stirring to a mixture of NaOH (5.0 g, 0.125 mol) and di-*n*-butylsulfamide (obtained from the reaction of *n*-butylamine and sulfuryl chloride,[16] mp 118–120°, 12 g, 0.058 mol) in 20 ml of pentane and stirred 2 hr at 25°. The mixture was extracted with three 50-ml portions of pentane and the pentane layer was dried ($MgSO_4$) and concentrated. The residue was distilled at 77° (30 mm) giving 5.0 g (59%) of azo-*n*-butane: ir (CCl_4) 2960, 2865, 1465, 1430, 1380 cm^{-1}; nmr (CCl_4) 3.72 ppm (4 H, triplet), 2.0–0.8 ppm (14 H, multiplet).

Azoxy-*n*-butane (11b).—To a solution of azo-*n*-butane (4.0 g, 0.028 mol) in methylene chloride (50 ml) was added a peracetic acid solution (10 ml, 4.9 *M* peracid in acetic acid) dropwise. The mixture was stirred for 2 hr at 0–10° and poured into 200 ml of water. The layers were separated, and the methylene chloride layer was washed with saturated aqueous solutions of $NaHSO_3$, $NaHCO_3$, and NaCl in 200-ml portions and dried ($MgSO_4$). Concentration and distillation [105° (20 mm)] gave azoxy-*n*-butane (**11b**) (2.09 g, 35%): ir (CCl_4) 2950, 2925, 2860, 1500, 1460, 1450, 1430, 1419, 1315, 1205 cm^{-1}; nmr (CCl_4) 4.17 (2 H, triplet), 3.37 (2 H, triplet), 2.0–0.8 ppm (14 H, multiplet); uv (EtOH) λ_{max} 218 mμ (ϵ 8088), 278 (53).

Anal. Calcd for $C_8H_{18}N_2O$: C, 60.76; H, 11.39; N, 17.72. Found: C, 60.70; H, 11.49; N, 17.85.

2,3-Diazabicyclo[2.2.1]-2-heptene N-Oxide (14).—A solution of 2,3-diazabicyclo(2.2.1]-2-heptene[17] (288 mg, 3.0 mmol) in methylene chloride (10 ml) was added at 0° to a methylene chloride (15 ml) solution of 85% *m*-chloroperbenzoic acid (800 mg, 4.0 mmol) and stirred at 25° for 3 hr. Neutralization (by 8 g of K_2CO_3, and stirring at room temperature for an additional 16 hr), filtration, and concentration at reduced pressure yielded 200 mg (57%) of crude **14**. Pure material (mp 87–89°) could be obtained either by sublimation, by recrystallization from hexane, or by collection from glpc. Azoxy compound **14** has the following spectral properties: ir ($CHCl_3$) 3000, 2960, 1500 (s), 1465, 1365, 1352, 1300 (w), 1285, 1252, 1180, 1121 cm^{-1}; uv (EtOH) λ_{max} 228 (ϵ 6000); nmr[18] ($CDCl_3$) 4.61 (2 H, singlet), 2.30–1.50 ppm (6 H, multiplet); mass spectrum, *m/e* (relative intensity), 112 (32, molecular ion), 68 (100), 67 (74), 39 (30).

Anal. Calcd for $C_5H_8N_2O$: C, 53.57; H, 7.14; N, 25.00; mol wt, 112. Found: C, 53.56; H, 7.13; N, 25.02; mol wt (cryoscopic in benzene), 122.

Di-*t*-butyloxadiaziridine (12a).—Azoxy-*t*-butane (**11a**)[18] [1,1-1′,1′-tetramethylazoxybutane] (12.0 g, 0.076 mol) was irradiated in 250 ml of purified pentane using a Hanovia Type L high-pressure lamp. The quartz inner-well was cooled with cold water. The solution was degassed (N_2 stream) and the photolysis was followed by disappearance of the uv band at 221 mμ (complete in 3 hr). The pentane was removed at reduced pressure at room temperature yielding a residue of crude di-*t*-butyloxadiaziridine (**12a**), 9.0 g. Analysis by glpc (5 ft × 0.25

(15) For a study of the effect of strong acids on primary and secondary azoxyalkanes, see R. Biela, H. Horing, and W. Pritzkow, *J. Prakt. Chem.*, **36**, 197 (1967); see also B. W. Langley, B. Lythgoe, and L. S. Rayner, *J. Chem. Soc.*, 4191 (1952).

(16) E. Schmitz and R. Ohme, *Angew. Chem. Int. Ed. Engl.*, **4**, 433 (1965).

(17) S. G. Cohen, R. Zand, and C. Steel, *J. Amer. Chem. Soc.*, **83**, 2895 (1961). In this preparation, it is necessary to follow exactly Cohen's procedure for the hydrolysis of the diester to the hydrazo compound. Oxidation of the hydrazo compound to the title compound was most efficiently accomplished by the copper(I) chloride method cited by Cohen.

(18) J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).

in., 20% SE-30, 100°) showed one major peak, which was collected and had infrared spectrum and retention time identical with those of azoxy-*t*-butane.

Small portion of **12a** (0.3–0.5 g) were purified one at a time by trap-to-trap distillation at room temperature and 0.1 mm. The distillation gave a mixture of di-*t*-butyloxadiaziridine (**12a**) and azoxy-*t*-butane (**11a**), the latter forming during work-up and distillation. This mixture was separated by chromatography on alumina using a water-cooled column and a 100:1 alumina: substrate ratio with pentane as eluent (order of elution: oxadiaziridine, azoxy-*t*-butane). The chromatography was successful with Woelm activity grade I neutral alumina and Merck acid-washed alumina. Di-*t*-butyloxadiaziridine (**12a**) has the following physical properties: nmr (CCl_4) 1.00 ppm (singlet); ir (CCl_4) 2970, 2925, 2850, 1475, 1452, 1380, 1365, 1230, 1205 cm^{-1}; mass spectrum *m/e* (relative intensity) 87 (7), 57 (100), 41 (40).

Anal. Calcd for $C_8H_{18}N_2O$: C, 60.76; H, 11.39; N, 17.72; mol wt, 158. Found: C, 60.62; H, 11.33; N, 17.70; mol wt (cryoscopic in benzene), 166.

Di-*n*-butyloxadiaziridine (**12b**) was prepared using the same procedure as for **12a**, above. After 2 hr of irradiation the ultraviolet maxima had disappeared. Removal of solvent and analysis of the mixture by glpc (5 ft × 0.25 in., 20% SE-30, 100°) showed two major peaks corresponding in retention time to azo-*n*-butane (14%) and azoxy-*n*-butane (**11b**) (86%). Chromatography on alumina (alumina:substrate = 100:1, pentane: methylene chloride eluent 50:50) resulted in elution of di-*n*-butyloxadiaziridine (**12b**) as the first fraction. Samples were found to be contaminated with 10% azo-*n*-butane. Trap-to-trap distillation of the crude mixture at 25° (0.01 mm) resulted in separation of di-*n*-butyloxadiaziridine (**12b**) and azo-*n*-butane from azoxy-*n*-butane (**11b**). Samples free of azo compound were prepared by rapidly mixing the crude mixture with *m*-chloroperbenzoic acid solution at 0° in methylene chloride and working up quickly at 0°. This converted azo-*n*-butane to azoxy-*n*-butane (**11b**) which was then separated from di-*n*-butyloxadiaziridine (**12b**) by either chromatography or distillation. Spectral properties: nmr (CCl_4) 2.63 ppm (4 H, triplet), 0.8–2.0 (14 H, multiplet); ir (CCl_4) 2945, 2915, 2857, 1466, 1387 cm^{-1} (infrared and nmr spectra identical with those of azoxy-*n*-butane were obtained by heating a sample at 90° for 4 min).

Anal. Calcd for $C_8H_{18}N_2O$: C, 60.76; H, 11.39; N, 17.72. Found: C, 60.58; H, 11.38; N, 17.67.

Photolysis of N-*t*-butyl-N′-methyldiimide N-oxide (1,1-dimethylethaneazoxymethane) (**11c**)[18,19] was carried out under the same conditions described for **12a** and **12b** [1.5 g (0.013 mol) of **11c** in 250 ml of pentane]. The uv max of **11c** disappeared after 2.5 hr. Concentration yielded a residue of 0.5 g, shown by glpc (5 ft, 20% SE-30, 100°) to be a mixture of at least 11 components: 50% corresponded to a mixture of two unsymmetrical azoxy compounds and 1-methyl-2-*t*-butyloxadiaziridine (**12c**), 22% was a mixture of low-boiling components, and 27% was a mixture of less volatile material. The infrared spectrum of the crude mixture showed characteristic azoxy bands, which increased in intensity on heating of a sample in a sealed tube for 5 min at 90°. The nmr of the crude material showed, in addition to a multiplet at 1.40–1.10 ppm, singlets at 3.10 ppm (3 H), 2.62 (3 H), 1.50 (9 H), and 1.00 (9 H). After standing overnight, the signals at 2.62 and 1.00 ppm (**12c**) disappeared with enhancement of the peaks at 3.10 and 1.50 ppm (**11c**). A weak signal was also observed at 3.95 ppm. Alumina chromatography yielded the high-boiling components of the mixture as a first fraction (elution with pentane). A second pentane fraction contained a complex mixture of products. Elution with methylene chloride yielded the azoxy compound. The nmr spectrum of the less volatile components showed a multiplet between 1.0 and 1.4 ppm. No signals were observed further downfield. This excludes dimers with N-methyl linkages.

Photolysis of 2,3-Diazabicyclo[2.2.1]-2-heptene N-Oxide (**14**). —A degassed solution of **14** (15 mg, 0.13 mmol) in 250 ml of spectroquality cyclohexane was irradiated with a Hanovia Type L high-pressure lamp. After 0.5 hr, the ultraviolet maximum due to the azoxy compound had disappeared. Heating of a portion of the photolysis solution at reflux for 0.5 hr effected no return of the azoxy ultraviolet absorption. Concentration under reduced pressure yielded a residue (13 mg) which contained some solid material which did not melt below 300°. Attempted sublimation of the residue was unsuccessful. Examination of the residue by glpc (8 ft × 0.25 in., 20% SE-30, 150°) showed no peaks other than solvent. Photolysis in Freon (188 mg **14** in 250 ml) and in octane (100 mg **14** in 250 ml) gave essentially the same results. Neither cyclopentene nor bicyclopentane was observed by glpc of the photolysis solution (octane solvent).

Isomerizations of Di-*t*-butyloxadiaziridine and Di-*n*-butyloxadiaziridine.—Isomerization of di-*t*-butyloxadiaziridine to axoxy-*t*-butane can be followed by nmr (disappearance of singlet at 1.00 ppm with appearance of singlets at 1.25 and 1.46 ppm), ir (appearance of bands at 1500 and 1300 cm^{-1}), and uv (appearance of band at 221 mμ). In the case of di-*n*-butyloxadiaziridine, the triplet centered at 2.60 ppm disappears with appearance of two triplets centered at 3.40 and 4.17 ppm. The thermal isomerization of di-*t*-butyloxadiaziridine was found to be essentially quantitative by comparison of the intensity of the ultraviolet absorption at 221 mμ after isomerization (ε 5501) with that of azoxy-*t*-butane (ε 5535). Analysis of this material by vpc (5 ft × 0.25 in., 20% SE-30, 100°) showed only one peak, identical in retention time and infrared spectrum with those of azoxy-*t*-butane. The rates of isomerization of di-*t*-butyloxadiaziridine and di-*n*-butyloxadiaziridine were followed by integration of nmr peaks, and the half-lives reported in the text for the thermal reaction were obtained from first-order plots.

Reactions with Trifluoroacetic Acid. A. Azoxy-*t*-butane (50 mg, 0.32 mmol) was mixed with 2.5 ml of trifluoroacetic acid. An immediate exothermic reaction took place with evolution of gas. Nmr of the solution showed a singlet at 1.47 ppm. The mixture was diluted with H_2O and extracted with ether. The ether phase was washed (saturated aqueous K_2CO_3), dried ($MgSO_4$), and concentrated. The residue (vpc, one peak) was identified as *t*-butyl trifluoroacetate by comparison of retention time and ir and nmr spectra with those of an authentic sample. The yield was 92% (based on 2 mol of *t*-butyl trifluoroacetate produced for every 1 mol of azoxy-*t*-butane consumed).

B. Di-*t*-butyloxadiaziridine (24.0 mg, 0.15 mmol) was added slowly to 0.5 ml of trifluoroacetic acid. Reaction took place immediately and resulted in formation of *t*-butyl trifluoroacetate (84% yield).

C. Azoxy-*n*-butane (50 mg, 0.32 mmol) was added to trifluoroacetic acid (0.5 ml). Some heat was evolved, but there was no evolution of gas as in the case of azoxy-*t*-butane. No change was observed in the nmr spectrum after 24 hr at room temperature. It should be noted, however, that the chemical shift of the methylene groups adjacent to the azoxy functionality is somewhat different in trifluoroacetic acid (3.83 and 4.66 ppm) than in a neat sample (3.40 and 4.17 ppm)].

D. Di-*n*-butyloxadiaziridine (50 mg, 0.32 mmol) was mixed with trifluoroacetic acid (0.5 ml) at 0° in an nmr tube and allowed to come to 20°. The oxadiaziridine gradually disappeared over a period of 80 min with appearance of triplets at 3.83 and 4.66 ppm, corresponding to azoxy-*n*-butane. In addition to this, two smaller triplets were observed centered at 4.20 and 4.69 ppm. The acid was destroyed by addition of solid K_2CO_3. Concentration yielded 47 mg of material which showed 80% azoxy-*n*-butane by glpc (5 ft × 0.25 in., 20% SE-30, 100°) in addition to 20% material of shorter retention time, which remains unidentified.

Reactions with Lithium Aluminum Hydride. A. Di-*t*-butyloxadiaziridine (100 mg, 0.63 mmol) was added at room temperature to a slurry of lithium aluminum hydride (40 mg, 1.0 mmol) in ether (5 ml). No signs of reaction were observed. Stirring was continued at room temperature for 1 hr and the mixture was quenched by cautious addition of H_2O. The ether phase was dried ($MgSO_4$) and concentrated, yielding 60 mg of material which was a mixture of di-*t*-butyloxadiaziridine (40%) and azoxy-*t*-butane (60%) by nmr. When **azoxy-*t*-butane** was subjected to the same conditions, it was recovered unchanged.

B. Azoxy-*n*-butane (510 mg, 3.2 mmol) was added in portions at room temperature to a slurry of lithium aluminum hydride (192 mg, 5.0 mmol) in 25 ml of ether. There was a slightly exothermic reaction for the first 20 min. Stirring was continued for 50 min more. The reaction mixture was quenched by cautious addition of H_2O. The ether phase was dried ($MgSO_4$) and concentrated yielding 364 mg (80%) of azo-*n*-butane, identified by comparison of infrared and nmr spectra with those of authentic material.

C. Di-*n*-butyloxadiaziridine was converted to azo-*n*-butane in 40% yield under the above conditions.

(19) J. G. Aston and D. M. Jenkins, *Nature*, **167**, 863 (1951).

Reaction of Di-*t*-butyloxadiaziridine with Sodium Iodide in Acetone. A. Titration.—Di-*t*-butyloxadiaziridine (21 mg, 0.13 mmol) was added to a degassed, saturated solution of sodium iodide in acetone (10 ml) containing 1 ml of 1.0 *N* HCl. An immediate dark red color appeared and the solution was stirred for 5 min at room temperature under N_2. Titration of the iodine with 0.020 *N* $Na_2S_2O_3$ solution gave an average value of 90% "active oxygen" for samples known to contain 90% di-*t*-butyloxadiaziridine by uv spectrum. When this procedure was employed with azoxy-*t*-butane as substrate, some coloration of the solution (yellow) was observed.

B. Product Identification.—Di-*t*-butyloxadiaziridine (100 mg, 0.63 mmol) was added at room temperature to a saturated solution of sodium iodide in acetone containing 1 drop of concentrated HCl. The mixture was stirred for 5 min at room temperature. The red color was dissipated by addition of a few drops of saturated aqueous $Na_2S_2O_3$. The ether layer was washed (aqueous NaOH) and examined by glpc (5 ft × 0.25 in., 20% SE-30, 100°). The yield of azo-*t*-butane was 95% by calibration with a known amount of decane.

Reactions with Methyllithium. A. Di-*t*-butyloxadiaziridine (146 mg, 0.92 mmol) was added at room temperature under N_2 to a stirred ether solution of methyllithium (1.25 ml of a 1.6 *N* solution). Stirring was continued for 1 hr at room temperature and the mixture was quenched by cautious addition of H_2O. Drying ($MgSO_4$) and concentration yielded 96 mg (65%) of a mixture of azoxy-*t*-butane, azo-*t*-butane, and di-*t*-butyloxadiaziridine in the ratio of 63:10:27 by integration of nmr peaks. Subjection of azoxy-*t*-butane to these conditions resulted in 9% reduction to azo-*t*-butane after 18 hr at room temperature.

B. Azoxy-*n*-butane (125 mg, 0.79 mmol) was added at 0° under N_2 to an ether solution of methyllithium (2.0 ml, 1.6 *M*). A vigorous reaction took place with evolution of gas and development of an orange color. After the bubbling had ceased (5 min), the reaction mixture was quenched by cautious addition of H_2O. Drying ($MgSO_4$) of the ether phase and concentration yielded a residue (66 mg) which was analyzed by glpc (2 ft × 0.25 in., 20% SE-30, 80°).

There were four peaks having relative retention times (intensity) of 0.43 (60%), 0.67 (2%), 0.86 (14%), and 1.0 (24%). The 14 and 24% peaks are thought to be the corresponding C_9 hydrazones. The mass spectrum of the 24% peak shows a molecular ion of 156 and the ir spectrum of the combined peaks shows NH absorption and a weak –C=N band. The nmr of the crude mixture shows a triplet centered at 6.83 ppm corresponding to the "aldehydic" hydrogen of the hydrazone. The 60% peak was identified as 1-methylazobutane (15) by comparison of its spectral properties with those of an authentic sample prepared by the method of Spialter:[20] ir (CCl_4) 2980, 2940, 2880, 1465, 1455, 1375 cm^{-1}; nmr (CCl_4) 3.66 ppm [triplet (2 H) superimposed on a multiplet (1 H)], 2.0–0.8 ppm, [multiplet (17 H) which includes a doublet (J = 6 cps) centered at 1.15 ppm]; mass spectrum m/e (relative intensity) 156 (9, molecular ion), 71 (47), 57 (36), 43 (100), 41 (39).

Anal. Calcd for $C_9H_{20}N_2$: C, 69.23; H, 12.82. Found: C, 69.15; H, 12.72.

C. Di-*n*-butyloxadiaziridine (82 mg, 0.52 mmol) was added at 0° under N_2 to a solution of methyllithium in ether (1.6 ml, 1.6 *M*). There was no color change or evolution of gas. Stirring was continued for 5 min and the mixture was quenched by cautious addition of H_2O. The ether phase was dried ($MgSO_4$) and concentrated yielding a residue of 49 mg. Analysis of this mixture by glpc (2 ft × 0.25 in., 20% SE-30, 80°) and nmr indicated that it was a mixture of azo-*n*-butane (75%) and *n*-butyraldehyde *n*-butylhydrazone (25%). The latter was identified by comparison with an authentic sample obtained by the method of Beringer.[21]

Conditions Which Gave No Reaction with the Oxadiaziridine and Azoxy Systems.—(a) Azoxy-*t*-butane and di-*t*-butyloxadiaziridine were recovered unchanged (except for isomerization of the latter) after stirring with magnesium and ethanol at room temperature for 24 hr. (b) Azoxy-*t*-butane and di-*t*-butyloxadiaziridine were recovered unchanged (except for isomerization) after stirring with triethyl phosphite for 24 hr at room temperature. (c) Azoxy-*t*-butane, azoxy-*n*-butane, di-*t*-butyloxadiaziridine, and di-*n*-butyloxyadiaziridine were shown to be inert to further oxidation by *m*-chloroperbenzoic acid (3–6 hr, room temperature, in CH_2Cl_2). (d) Azoxy-*t*-butane, azoxy-*n*-butane, di-*t*-butyloxadiaziridine, and di-*n*-butyloxadiaziridine could be recovered unchanged (except for isomerization) after 3 hr of stirring in an ethanol solution at room temperature under 1 atm of hydrogen with 10% Pd–C as catalyst. (e) Azoxy-*t*-butane was recovered unchanged after stirring for 24 hr at room temperature with 6 *M* aqueous NaOH. Di-*t*-butyloxadiaziridine showed only isomerization to the azoxy compound under these conditions. (f) Di-*n*-butyloxadiaziridine did not undergo reaction at room temperature with furan, norbornylene, phenyl isocyanate, or diazomethane.

Registry No.—**11a**, 16649-52-8; **11b**, 17697-56-2; **12a**, 18857-00-6; **12b**, 24766-60-7; **14**, 22509-00-8; **15**, 24766-62-9.

(20) L. Spialter, D. H. O'Brien, G. L. Untereiner, and W. A. Rush, *J. Org. Chem.*, **30**, 3278 (1965).

(21) F. M. Beringer, J. A. Farr, Jr., and S. Sands, *J. Amer. Chem. Soc.* **75**, 3984 (1953).

Reactions of Pyridinium Salts with Alkaline Hydrogen Peroxide. Formation of Pyrrolidinone Hydroperoxides from 1-Methyl- and 1-Benzyl-3-carbamoylpyridinium Chloride[1,2]

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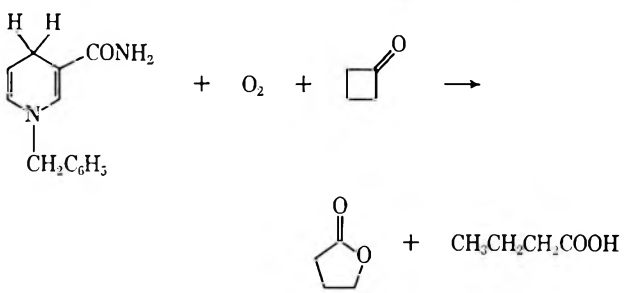
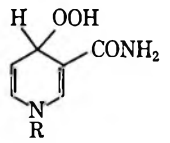
An attempt to prepare a hydroperoxide adduct of 1-methyl- (or 1-benzyl-) 3-carbamoylpyridinium chloride by treatment of the salt with alkaline hydrogen peroxide results in the formation of pyrrolidinone hydroperoxides, **2a** and **2b**, the end products of an extensive rearrangement. Yields are low (7–8%), but the products are obtained in good purity from readily available starting materials. The structure of the hydroperoxide derived from the 1-methyl salt was established by its conversion to N-methyl-N-[(1-methyl-2-oxo-3-pyrrolidinyl)methyl]formamide (**6**), which was synthesized independently from 1-methyl-2-pyrrolidinone. The structure of the corresponding pyrrolidinone from the 1-benzyl salt is inferred from its physical and chemical similarities to the methyl derivative. Treatment of 1-benzyl-3-acetylpyridinium chloride with alkaline hydrogen peroxide gives N-benzylformamide in low yield, and similar treatment of the 3-bromo derivative gives N-benzyl-2,2-dibromoacetamide, also in low yield. The infrared, ultraviolet, nmr, and mass spectra of the new pyrrolidinone derivatives are discussed, and a possible mechanism for the rearrangement is presented.

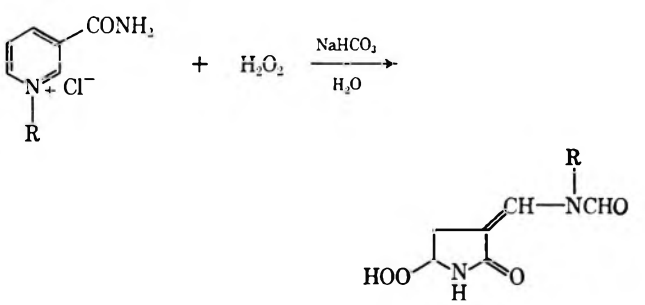
In a study of the reducing properties of 1-benzyl-1,4-dihydronicotinamide, a model for the coenzyme NADH (reduced nicotinamide–adenine dinucleotide), the oxidation of cyclobutanone to butyrolactone and butyric acid in low yield was observed in the presence of oxygen and the dihydronicotinamide.[3] No reaction occurred in the absence of oxygen or the nicotinamide derivative. When the bright lemon-yellow dihydronicotinamide was exposed to air, it became orange; this orange material when treated with cyclobutanone also gave butyrolactone and butyric acid. The dihydronicotinamide apparently is acting as an oxygen carrier in the reaction, and, because of the importance of oxidations in living systems in which the pyridine coenzymes play a role,[4] the identification of oxygen-rich intermediates derived from the coenzyme model was attempted. A possible intermediate in the reaction of oxygen, cyclobutanone, and 1-benzyl-1,4-dihydronicotinamide is a hydroperoxide of dihydronicotinamide such as 4-hydroperoxy-1-alkyl-1,4-dihydronicotinamide, **1**.[5] An attempt to synthesize such an intermediate by the reaction of the pyridinium salt with hydroperoxide anion was unsuccessful, but a new, stable hydroperoxide was obtained which may be of interest in possible metabolic paths for the degradation of the pyridine coenzymes in the presence of cellular hydrogen peroxide.[6]





1

Treatment of 1-Methyl- or 1-Benzyl-3-carbamoylpyridinium Chloride with Alkaline Hydrogen Peroxide.—A white solid of molecular formula $C_7H_{10}N_2O_4$ or $C_{13}H_{14}N_2O_4$ precipitated slowly (1–3 months for the former, 6 days for the latter) when 1-methyl- or 1-benzyl-3-carbamoylpyridinium chloride, respectively, was treated with excess 30% hydrogen peroxide and 1 equiv of sodium bicarbonate at 0–5°. The compounds are hydroperoxides: they oxidize iodide ion to iodine, show absorption in the infrared at 837–841 cm^{-1} for a hydroperoxy group,[7] show a base peak in the mass spectrum caused by loss of hydrogen peroxide plus carbon monoxide, and show absorption in the nmr spectrum at δ 11.54–11.56 (dimethyl sulfoxide-d_6).[8] The structures of the hydroperoxides were shown to be **2a** (N-



2a, R = CH_3
b, R = $C_6H_5CH_2$

(1) This work was aided by Grant AM-07770 of the National Institutes of Health, U. S. Public Health Service, which we acknowledge with gratitude.

(2) For complete details, see D. W. Bristol, Ph.D. Thesis, Syracuse University, 1969. Also see D. W. Bristol and D. C. Dittmer, Abstracts, 158th National Meeting of the American Chemical Society, Division of Organic Chemistry, New York, N. Y., Sept 1969, No. 150.

(3) D. C. Dittmer, R. A. Fouty, and J. R. Potoski, *Chem. Ind.* (London), 152 (1964).

(4) "Oxygenases," O. Hayaishi, Ed., Academic Press, New York, N. Y., 1962.

(5) Recently, **1** was proposed as a possible intermediate in the reaction of 1-benzyl-1,4-dihydronicotinamide with oxygen in the presence of phenazine or cupric ions: L. S. Negievich, O. M. Grishin and A. A. Yasnikov, *Ukr. Khim. Zh.*, **34**, 381 (1968); *Chem. Abstr.*, **69**, 76221 (1968).

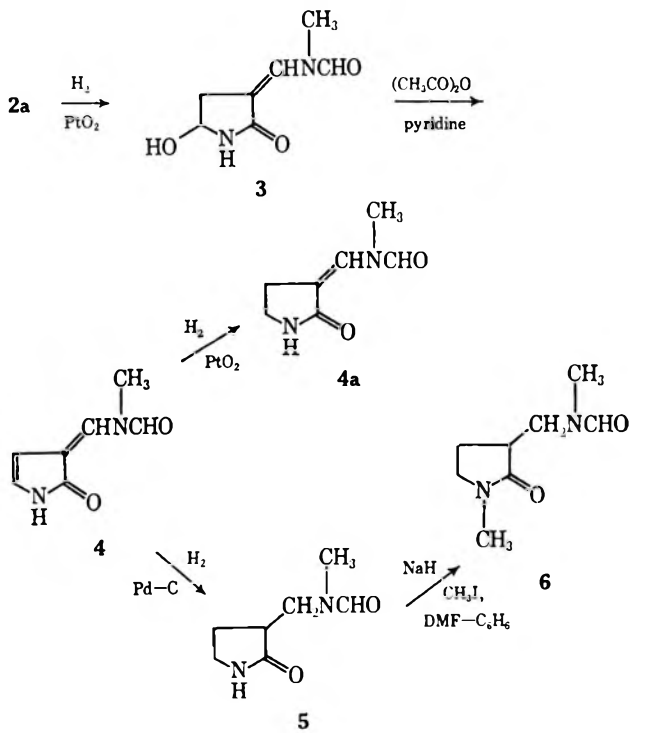
(6) Organic peroxides inhibit the growth of ascites tumors: C. Weitzel, E. Buddecke, F. Schneider, and H. Pfeil, *Z. Physiol. Chem.*, **325**, 65 (1961); B. Weitzel, E. Buddecke and F. Schneider, *ibid.*, **323**, 211 (1961).

(7) B. F. Sagar, *J. Chem. Soc., B*, 428 (1967).

(8) Loss of hydrogen peroxide is observed in the mass spectra of simple hydroperoxides: A R. Burgess, R. D. G. Lane, and D. K. Sen Sharma, *ibid., B*, 341 (1969). A nmr spectrum of cumene hydroperoxide in dimethyl sulfoxide-d_6 has absorption at δ 11.2. Two N-alkylamide hydroperoxides show absorption at δ 10.80 in acetone-d_6 (ref. 7).

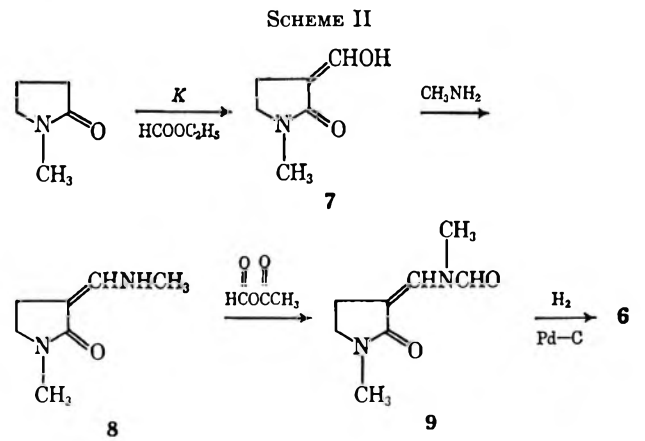
[(5-hydroperoxy-2-oxo-3-pyrrolidinylidene)methyl]-N-methylformamide)[9] and **2b** (N-benzyl-N-[(5-hydroperoxy-2-oxo-3-pyrrolidinylidene)methyl]formamide or 3-benzylformamidomethylene-5-hydroperoxy-2-pyrrolidinone). The structure of the N-methyl derivative **2a** was deduced from its conversion to saturated pyrrolidinone **6** coupled with an independent synthesis of **6**. The structure of **2b** was deduced from physical and chemical analogies to **2a**. The degradation scheme of **2a** is outlined in Scheme I, and an independent synthe-

SCHEME I



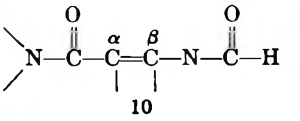
sis of **6** from 1-methyl-2-pyrrolidinone is given in Scheme II. Pertinent points about the degradation,

SCHEME II



synthesis, and the physical properties of this class of pyrrolidinone derivatives are discussed below.

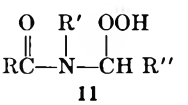
Properties of Hydroperoxides 2a and 2b.—The β-formamido-α,β-unsaturated amide group **10** occurs not only in the hydroperoxides but also in compounds **3**, **4**, **4a**, and the N-benzyl analog of **3**. All of these



10

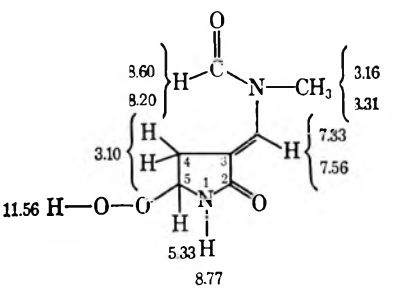
derivatives show intense ultraviolet absorption near 264 mμ (ε ~ 20,000) and characteristic infrared absorption around 1700–1720 (formyl carbonyl stretching vibration), 1671–1695 (pyrrolidinone carbonyl), and 1620–1635 cm^{-1} (carbon–carbon double bond).[10]

The average absorptions (δ) of the protons of **2a** observed in the nmr spectrum (dimethyl sulfoxide-d_6) are summarized in structure A. Those of **2b** are similar except for upfield shifts for the C-4 protons, and downfield shifts for the formyl and vinyl protons. The chemical shift of the 5-methine proton at δ 5.33 is comparable with the average value of δ 5.48 for the methine proton in N-alkylamide hydroperoxides **11**[7] indicates that the hydroperoxy group is at the 5 position rather than at the 4 position. Frequency sweep double res-



11

onance of the region at 3.10 ppm, at which the 4-methylene protons absorb, shows that these protons are coupled both to the methine proton at C-5 and to the vinyl proton.



A

The absorptions caused by the methyl (or benzyl), vinyl, and formyl protons of **2a**, **2b**, **5**, and **6** are split each into two components of unequal intensity which is caused by restricted rotation about the carbon–nitrogen bond of the formamido group and is characteristic of unsymmetrical N,N-disubstituted formamides.[11] Models indicate that the methyl group would prefer to be *trans* to the carbonyl group. The predominant rotamer in tertiary formamides is the one in which the bulkier group on nitrogen is *trans* to the carbonyl group.[11]

The melting points of **2a** and **2b** are sharp which indicates the probable absence of a mixture of geometrical isomers, and samples behave homogeneously on thin layer chromatography on silica gel with several solvents. The observation of a high absorptivity in the ultraviolet spectrum of **2a** and **2b**, favors a *trans* orien-

(9) We are indebted to Dr. Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, American Chemical Society, for assistance in naming **2** and its derivatives.

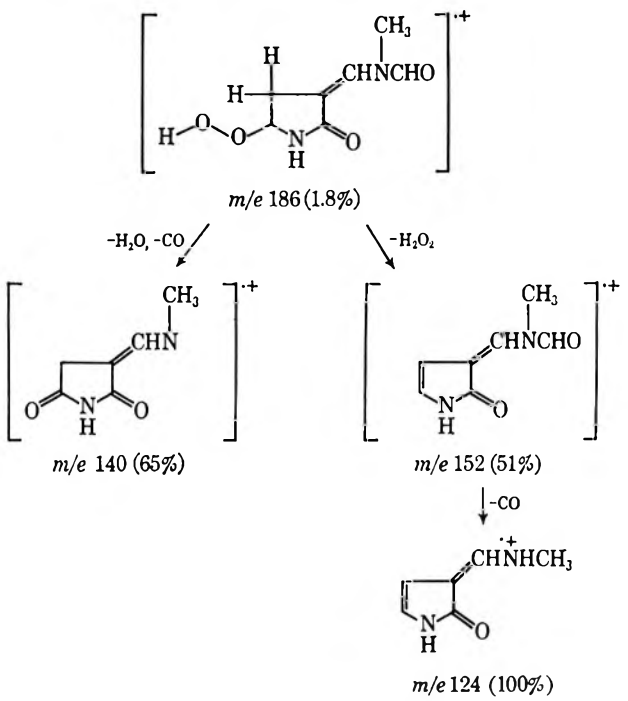
(10) These infrared absorptions may be the result of more complex vibrations than the simple stretching vibrations.

(11) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, p 553.

tation of amido groups.[12] Accordingly, only one double-bond isomer is believed to be formed, probably of the configuration shown in structure A.

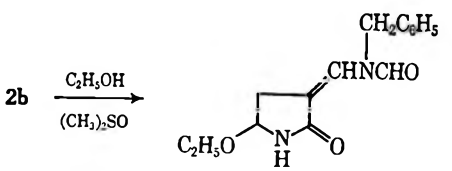
A rationalization of the major peaks of the mass spectrum of hydroperoxide **2a** is given in Scheme III.[13]

SCHEME III



The ion fragment *m/e* 124 also appears in the mass spectra of alcohol **3** ($M^+ - H_2O - CO$) and of diene **4** ($M^+ - CO$) which indicates the similarity of structure of these three compounds. The loss of carbon monoxide with rearrangement of the formyl proton is involved in the formation of the base peak in the mass spectra of each of the compounds containing chromophore **10**.[14] Similar fragmentations are observed for **2b**.

When **2b** is heated on a steam bath with ethanol and dimethyl sulfoxide, an ethyl ether is formed.



Conversion of Hydroperoxide 2a to N-Methylpyrrolidinone 6.—The hydroperoxy group of **2a** (or **2b**) is reduced to an hydroxyl group by 1 mol of hydrogen. Use of palladium on charcoal instead of platinum oxide results also in reduction of the carbon–carbon double bond to yield saturated alcohols. Ultraviolet absorption of alcohol **3** at 264 mμ (ε 21,200) and infrared absorptions at 1706, 1672, and 1620 indicate that chromophore **10** is still present.

The hydroxyl group of **3** is in the 5 rather than the 4 position because the chemical shift of the methine proton (δ 5.13) is at lower field than is typical for an unsubstituted secondary alcohol and this chemical shift is in good agreement with chemical shifts tentatively reported for the methylene protons of N-hydroxymethyl-N-methylformamide (δ 5.09) and N-hydroxymethyl-N-benzylformamide (δ 5.05).[15] Irradiation of the vinyl proton causes the absorption of the methylene group at C-4 to simplify but has no effect on the methine absorption, consistent with the hydroxyl group being at position 5.

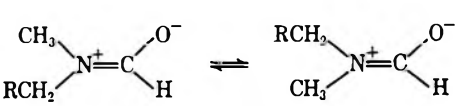
The mass spectrum of **3** shows a base peak for a fragment (*m/e* 124) corresponding to the loss of water and carbon monoxide from the molecular ion and an intense peak for a fragment (*m/e* 152) corresponding to the loss of water only from the molecular ion. Similar behavior occurs with the alcohol derived from **2b**.

Dehydration to the diene **4** occurs when alcohol **3** is treated with acetic anhydride in dry pyridine. Infrared nmr, and ultraviolet spectra show the presence of chromophore **10** and the pyrrolidinone ring. Two maxima, 263 mμ (ε 17,400) and 361 (7500), in the ultraviolet spectrum may be attributed to the cross-conjugated system in **4**.[16] The most abundant ion in the mass spectrum of **4** is at *m/e* 124 and is produced by loss of carbon monoxide from the parent ion.

Hydrogenation of diene **4** over palladium on charcoal gives completely reduced pyrrolidinone **5**. Selective hydrogenation of the carbon–carbon double bond in the ring occurs to give **4a** when platinum oxide was used as catalyst, the reaction being stopped after the uptake of 1 equiv of hydrogen. Treatment of saturated pyrrolidinone **5** with sodium hydride in dimethylformamide–benzene[17] yields the sodium salt which is methylated by treatment with methyl iodide to yield **6**.

The spectroscopic properties of **5** and **6** are similar. In the solid phase, absorption in the infrared spectrum of **5** occurs at 3200 (intermolecularly hydrogen-bonded N–H), 1705 (pyrrolidinone carbonyl), and 1660 cm^{-1} (formamide carbonyl) while in solution in carbon tetrachloride the corresponding absorptions are at 3445, 1713, and 1678 cm^{-1}.

The nmr absorption for the N-methyl protons of the formamido group of **5** and **6** appears as two lines of approximately equal intensity. Their separation is field and temperature dependent which indicates restricted rotation in the formamido group as observed in the other intermediates described above. The formyl proton was not affected by the rotational isomerism since its environment in the two rotamers is essentially the same. The absorption of the methylene protons [$-CH_2N(CH_3)CHO$] adjacent to the 3 position of the



(12) A *cis*-oriented model has a lower molar absorptivity: Sadtler Standard Ultraviolet Spectrum No. 5552, Sadtler Research Laboratories, Philadelphia, Pa., 1965.

(13) Intensities are given in terms of per cent of the base peak. Other structures for the ions may be written.

(14) Loss of carbon monoxide with rearrangement of the formyl proton is observed in the mass spectra of N-formyl-α-amino acid esters: K. Heyns and H.-F. Grützmacher, *Z. Naturforsch. B*, **16**, 293 (1961).

(15) J. P. Chupp and A. J. Speziale, *J. Org. Chem.*, **28**, 2592 (1963).

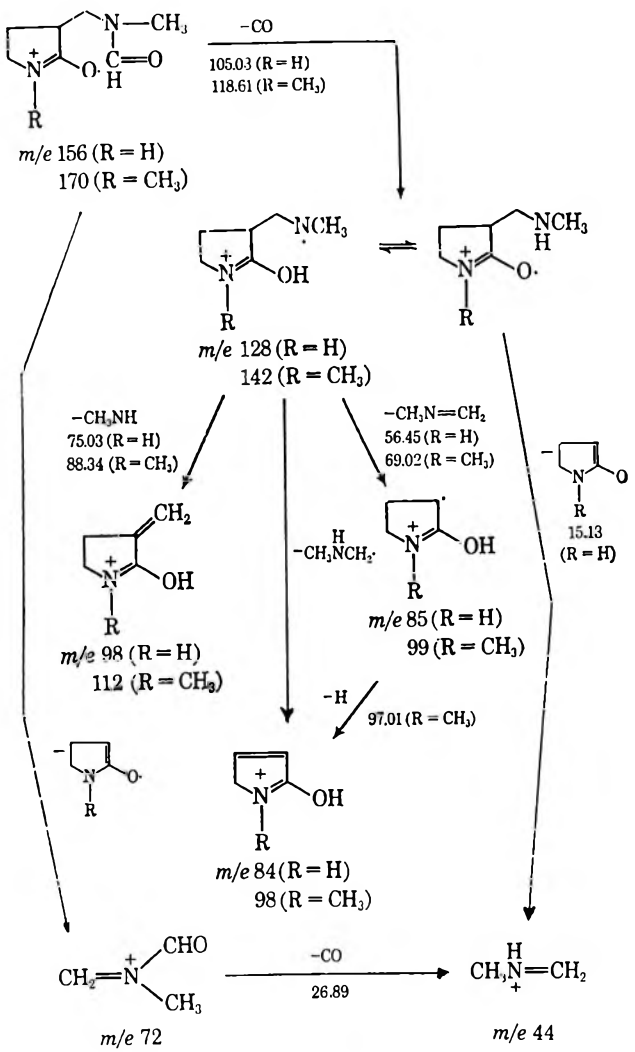
(16) 1-Alkyl-3-substituted 1,6-dihydropyridines which are cross conjugated show two maxima at longer wavelengths than observed for 1,4-dihydropyridine derivatives: K. Wallenfels and H. Schüly, *Justus Liebigs Ann. Chem.*, **621**, 136 (1959).

(17) The sodium salt is insoluble in dimethylformamide but addition of benzene results in dissolution of the salt. Without addition of benzene, no alkylated product is obtained with methyl iodide.

pyrrolidinone ring is complex and apparently comprises two sets of multiplets (each of which is the AB part of an ABX spectrum).

Use of the N-methyl group on the pyrrolidinone nitrogen in **6** as a label in mass spectrometry together with metastable ion transitions is helpful in interpretation of the mass spectra of **5** and **6** in terms of their structures. A rationalization of the important features of the mass spectra of **5** and **6** is outlined in Scheme IV.

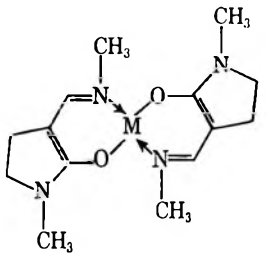
SCHEME IV



Other structures for the ions may be written in which charge is localized in the formamide group. Where metastable ion transitions were observed, the calculated *m/e* values are indicated in the scheme beside the arrows. Loss of carbon monoxide from the molecular ions of **5** and **6** is important but its loss from N,N-dimethylformamide is not,[18] possibly because there is no easy way to rearrange the formyl hydrogen in the latter.

Synthesis of 6 from 1-Methyl-2-pyrrolidinone.—Scheme II depicts the steps of the synthesis. The known enol, 3-hydroxymethylene-1-methyl-2-pyrrolidinone[19] (**7**), is treated with excess methylamine in dry ethanol to yield the enaminoamide **8**. The ultraviolet spectrum of **8** disappears on addition of 1 drop of dilute acid. Enaminoamide **8** is formed as a mixture of *cis* and *trans* isomers. The *cis* form appears to predominate in dilute solution while the *trans* form predominates in the solid phase.[20]

The enaminoamide forms an intense blue color with Fe^{III} ions and a green complex with Cu^{II} ions. Formation of a stable complex such as **12** may explain why the olefinic double bond could not be hydrogenated over platinum oxide or over 5% palladium on charcoal at atmospheric pressure.



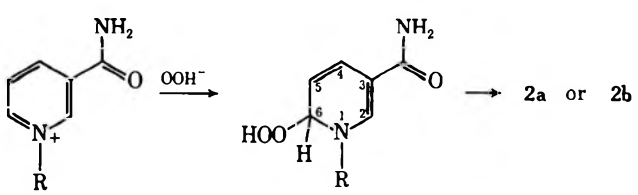
12

Formylation of **8** by formic–acetic anhydride gives **9**, whose spectra are similar to those of the partially hydrogenated product **4a** obtained from diene **4**.

The most abundant ion in the mass spectrum of **9** and enaminoamide **8** is at *m/e* 140. The fragmentation patterns of these compounds are very similar. These similarities may be attributed to the formation of an abundant ion of identical structure from either **9** or **8**.

Hydrogenation of **9** over palladium on charcoal gives 1-methylpyrrolidinone **6** whose properties were identical with those of the pyrrolidinone obtained by degradation of the product (**2a**) from 1-methyl-3-carbamoylpyridinium chloride and alkaline hydrogen peroxide.

Mechanistic Considerations.—In the reaction of the pyridinium salt with hydrogen peroxide in sodium bicarbonate, the pH of the solution decreases with time as carbon dioxide is evolved. This may be interpreted as a decrease in the concentration of hydroperoxide anion resulting from its addition to the pyridinium ring. Although addition can occur at either the 2, 4, or 6 positions, the structure of the product indicates that it probably arises from attack at the 6 position.[21] Enzymic oxidation of nicotinic acid occurs *via* oxidation of the 6 position.[22]



A possible mechanism which accounts for the formation of product **2** is given in Scheme V. An analogy is the reaction of 5,6-diphenyl-2,3-dihydropyrazine with

(18) Catalog of Mass Spectral Data, American Petroleum Institute Research Project 44, National Bureau of Standards, Serial No. 113, 1951. The base peak is caused by loss of HCO.

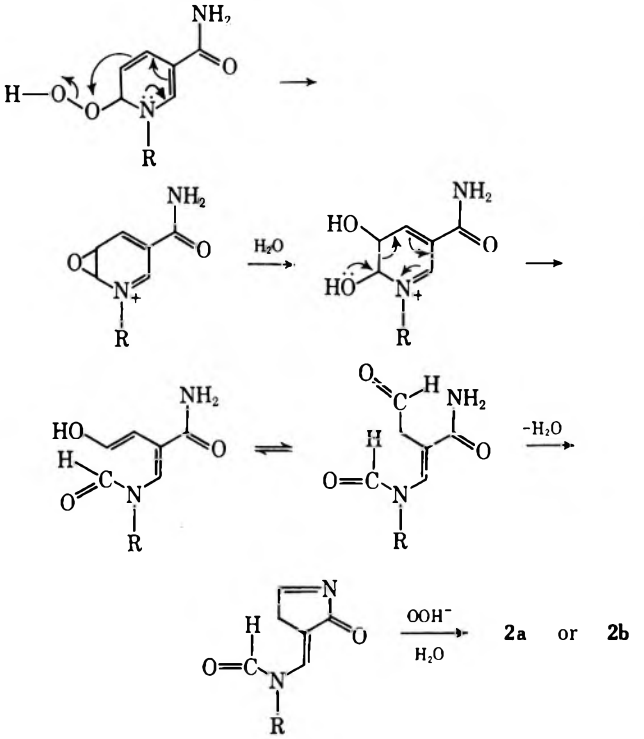
(19) K. H. Büchel and F. Korte, *Chem. Ber.*, **98**, 2465 (1962).

(20) *cis* and *trans* isomerism in similar compounds has been investigated by infrared and nmr: J. Dabrowski and U. Dabrowski, *ibid.*, **101**, 2365 (1968); G. O. Dudek and G. P. Volpp, *J. Amer. Chem. Soc.*, **85**, 2697 (1963).

(21) No product is formed when distilled, deionized water is used as solvent. Metal ions present in the tap water may catalyze the decomposition of the hydroperoxide adduct or the further oxidation of the ring. See A. R. Doumaux, Jr., J. E. McKeon, and D. J. Trecker, *ibid.*, **91**, 3992 (1969), for recent examples of metal-ion-catalyzed oxidations.

(22) D. A. Hughes, *Biochem. J.*, **60**, 303 (1955).

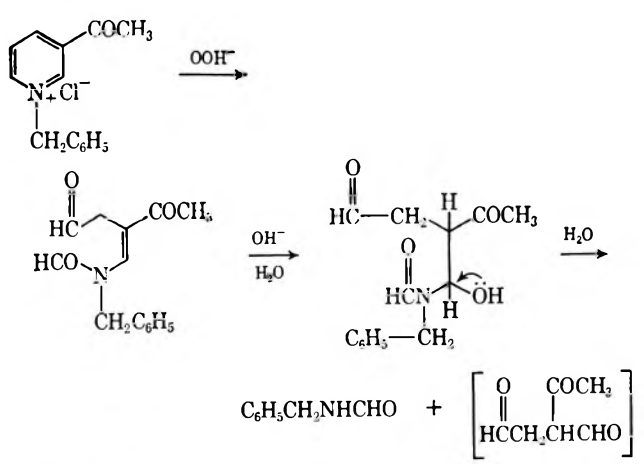
SCHEME V



methanolic hydrogen peroxide which also results in a ring opening and contraction to a five-membered ring.[23]

Treatment of 1-Benzyl-3-acetylpyridinium Chloride and 1-Benzyl-3-bromopyridinium Chloride with Alkaline Hydrogen Peroxide.—N-Benzylformamide was isolated in 6% yield on treatment of 1-benzyl-3-acetylpyridinium chloride with hydrogen peroxide and aqueous sodium bicarbonate, and N-benzyl-2,2-dibromoacetamide was obtained in 2% yield from 1-benzyl-3-bromopyridinium chloride. Traces of other oily products were obtained but were not identified.

N-Benzylformamide may be considered as arising from an intermediate analogous to that proposed in the decomposition of 1-methyl-3-carbamoylpyridinium chloride. Formation of N-benzyl-2,2-dibromoacetamide from 1-benzyl-3-bromopyridinium chloride may occur *via* bromination of N-benzyl-2-bromoacetamide[24] by molecular bromine produced by oxidation of bromide



ion formed by a displacement or elimination reaction from the pyridinium salt.

Experimental Section

Melting points were obtained on a Fisher-Johns melting point apparatus and are corrected unless otherwise indicated. Microanalyses were performed at Galbraith Laboratories, Knoxville, Tenn., or at Alfred Bernhardt Microanalytisches Laboratorium in Max-Planck-Institut für Kohlenforschung, Mülheim, West Germany. Molecular weights were determined by vapor pressure osmometry or by mass spectrometry. Infrared spectra were obtained on either a Perkin-Elmer Model 521 grating spectrophotometer or a Perkin-Elmer Model 137 sodium chloride spectrophotometer. The infrared absorptions are in cm^{-1} and the relative intensities are given as weak (w), medium (m), and strong (s). Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 ultraviolet-visible spectrophotometer. The absorptions are reported in mμ and their intensity (ε) in liter/mole centimeter. Proton nuclear magnetic resonance (nmr) spectra were obtained on either a Jeolco Model 4H-100 or a Varian Model A-60 nuclear magnetic resonance spectrometer. Chemical shifts are reported as δ values using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. The absorption position of a complex multiplet is reported as the center of the absorption. Abbreviations used in reporting nmr data in tables are b, broad; m, complex multiplet; s, singlet; d, doublet; t, triplet. Mass spectra were obtained on a Perkin-Elmer Hitachi Model RMU-6E single-focusing spectrometer. Only those peaks of mass greater than 29 and which are 5% or more of the base peak or which have special significance are reported. Thin layer chromatography (tlc) was performed according to standard methods[25] by use of either Eastman Chromatogram Sheet 6060 (silica gel) or 6063 (alumina) or apparatus from Brinkman Instruments, Inc., Westbury, N. Y., and Merck silica gel HF_{254}.

Reaction of 1-Methyl-3-carbamoylpyridinium Chloride with Hydrogen Peroxide and Sodium Bicarbonate. N-[(5-Hydroperoxy-2-oxo-3-pyrrolidinylidene)methyl]-N-methylformamide (2a).—Treatment of 1-methyl-3-carbamoylpyridinium chloride[26] (17.3 g, 0.100 mol) with 30% hydrogen peroxide (30.9 ml, 0.300 mol) (Baker and Adamson) and sodium bicarbonate (8.41 g, 0.100 mol) (Baker and Adamson, anhydrous) in tap water (110 ml) at 0–5° gave a pale yellow solution which had a pH of 8.0. After 8 days at 0–5°, the pH of the yellow solution was 5.0 and a white solid had begun to precipitate. After 3 months, the mixture was filtered and the solid was washed thoroughly with cold water and dried overnight under vacuum at room temperature to yield a granular, white solid (1.49 g, 8.0%). Reaction times of 1 month gave slightly lower yields. Two recrystallizations from 95% ethanol gave a white solid, mp 161–162° dec. Use of a tenfold excess of either 30 or 50% hydrogen peroxide did not affect the yield.

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05; mol wt, 186.2. Found: C, 45.20; H, 5.34; N, 14.92; mol wt, 190 (ethanol).

The compound was soluble in dilute sodium hydroxide solution and in triethylamine, gave a positive test for peroxide with potassium iodide–starch paper, decolorized bromine water and potassium permanganate solution, and gave a purple color with ferric chloride solution after treatment with a basic solution of hydroxylamine. Thin layer chromatography (Merck, silica gel HF_{254}) gave only one spot (solvent, R_f): chloroform, 0.00; 1:1 chloroform–ethanol, 0.31; ethanol 0.52; 95% ethanol, 0.65; water, 0.73; pyridine, 0.71. After the plate was developed and visualized in one direction, it was rotated 90° and developed again. Only a single spot was observed.

The following spectral properties were observed: uv max (95% ethanol) 264 mμ (ε 17,600); ir (KBr) 3400 (m), 3290 (s), 3240 (m), 3140 (m), 2940 (w), 2790 (w), 1717 (s), 1678 (s), 1635 (s), 1438 (m), 1430 (m), 1419 (m), 1395 (m), 1338 (m), 1298 (m), 1240 (s), 1213 (m), 1189 (m), 1107 (m), 1080 (s), 1068 (s), 1032 (m), 980 (m), 945 (w), 872 (m), 841 (m), 822 (w), 768 (m), 747 (m), 732 (m), 677 (m), 655 (m), 640 (m), 583 (m),

(23) H. I. X. Mager and W. Berends, *Recl. Trav. Chim. Pays-Bas*, **84**, 314 (1965).

(24) A speculative mechanism involving a 2-pyridone can be written for the formation of N-benzyl-2-bromoacetamide.

(25) J. Bobbitt, "Thin-Layer Chromatography," Reinhold Publishing Corp., New York, N. Y., 1963.

(26) P. Karrer, G. Schwarzenback, F. Benz, and U. Solmssen, *Helv. Chim. Acta*, **19**, 826 (1936).

and 512 (m) cm^{-1}; nmr (100 MHz, dimethyl sulfoxide-d_6) δ 11.56[27] (s, 0.93), 8.77[27] (broad, 1.0), 8.60 (s, 0.74), 8.20 (s, 0.26), 7.56 (t, 0.22), 7.33 (t, 0.78), 5.33 (m, 0.96), 3.10 (m), 3.31 (s), 3.16 (s, 4.9, combined with area of peaks at δ 3.10 and 3.31); nmr (100 MHz, pyridine-d_5) δ 13.7 (broad, 0.95), 10.2 (broad, 0.95), 8.67 (s, 0.87), 8.21 (s, 0.15), 8.36 (t, 0.23), 7.72 (t, 0.79), 5.83 (m, 1.00), 3.31 (m, 2.10), 3.09 (s, 2.94); mass spectrum (70 eV, direct inlet, ambient temperature) *m/e* (relative intensity) 186 (1.8), 170 (0.4), 169 (1.6), 168 (12.5), 158 (3.1), 153 (6.2), 152 (50.7), 142 (1.6), 141 (6.4), 140 (64.8), 139 (14.4), 126 (3.2), 125 (17.9), 124 (100), 123 (11.5), 112 (5.8), 111 (8.3), 109 (5.3), 99 (2.2), 98 (8.7), 97 (27.4), 96 (17.0), 95 (25.2), 94 (23.7), 93 (4.1), 84 (7.8), 83 (19.8), 82 (17.5), 81 (41.3), 80 (19.9), 70 (5.0), 69 (41.9), 68 (35.1), 67 (43.0), 66 (16.5), 59 (8.2), 58 (5.0), 57 (6.1), 56 (6.0), 55 (33.3), 54 (17.4), 53 (12.7), 52 (12.5), 51 (5.5), 46 (5.6), 45 (8.0), 44 (9.1), 43 (18.1), 42 (22.9), 41 (36.9), 40 (11.3), 39 (41.7), 38 (12.4), 36 (7.2), 34 (13.1), 33 (1.6), 32 (2.0), 31 (13.4), 30 (28.7).

N-Benzyl-N-[(5-hydroperoxy-2-oxo-3-pyrrolidinylidene)methyl]formamide (2b).—Treatment of 1-benzyl-3-carbamoylpyridinium chloride (9.96 g, 40.0 mmol) with 30% hydrogen peroxide (12.1 ml, 119 mmol, Baker and Adamson) and sodium bicarbonate (3.36 g, 40.0 mmol) (Baker and Adamson, anhydrous) in tap water (36 ml) gave a clear yellow solution, pH 8.5. The reaction mixture was refrigerated at 4° and an orange oil slowly separated on the bottom and sides of the flask. The pH of the solution decreased to 5. After 6 days, a small amount of white solid began to precipitate from the solution (pH 4.5). The oil and the precipitate were removed and the solution was returned to the refrigerator. The white solid continued to form and after 16 days it was removed by filtration and dried for 24 hr under vacuum at room temperature to give 0.40 g of solid, mp 133–140° cor. Addition of cold 95% ethanol to the oil and solid obtained by filtration caused the oil to dissolve, and an additional 0.24 g of crude white solid was obtained. The total yield of crude product was 6.1%. Three recrystallizations from absolute ethanol gave a white solid, mp 142.5–145° dec with evolution of gas.

When the benzylpyridinium salt was treated with a tenfold excess of 30% hydrogen peroxide, the reaction occurred without the formation of orange oil. After 6 days, a white solid began to form and the pH of the solution had changed from 8.5 to 5.0. Work-up gave relatively pure solid (7.3%) which was identical with that obtained above.

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68; mol wt, 262. Found: C, 59.63; H, 5.46; N, 10.63; mol wt, 266 (ethanol), 237 (tetrahydrofuran).

The following spectral properties were observed: uv max (95% ethanol) 264 mμ (ϵ 18,500); ir (KBr) 3400 (m, shoulder), 3240 (s), 3065 (w), 3035 (w), 2937 (w), 2905 (w), 1720 (s), 1688 (s), 1635 (s), 1498 (m), 1452 (m), 1404 (m), 1318 (m), 1265 (s), 1210 (m), 1159 (s), 1090 (m), 1077 (m), 1028 (w), 974 (m), 911 (m), 839 (m), 775 (w), 743 (w), 716 (m), 693 (w), 677 (w), 582 (w), 521 (w), and 462 (w) cm^{-1}; mass spectrum (70 eV, direct inlet, 150°) *m/e* (relative intensity) 262 (0.0), 244 (6.2), 229 (4.1), 228 (10.3), 217 (15.5), 216 (92.8), 215 (50.5), 201 (22.7), 200 (100), 199 (14.4), 171 (12.4), 156 (12.4), 145 (18.1), 144 (35.0), 143 (18.6), 142 (11.3), 135 (61.9), 134 (39.6), 130 (10.3), 128 (10.7), 118 (10.3), 117 (16.5), 116 (12.0), 115 (19.8), 109 (14.4), 107 (13.4), 106 (59.8), 105 (16.1), 104 (25.4), 95 (11.3), 94 (11.3), 93 (10.3), 92 (72.5), 91 (3210), 90 (24.7), 89 (37.1), 83 (10.9), 82 (24.7), 81 (19.6), 80 (10.3), 79 (37.1), 78 (22.7), 77 (43.3), 73 (11.3), 69 (15.5), 68 (14.4), 67 (20.6), 66 (21.6), 65 (177), 64 (18.6), 63 (47.4), 62 (12.4), 57 (14.4), 55 (35.0), 54 (37.1), 53 (28.9), 52 (41.2), 51 (69.1), 50 (30.9), 46 (14.4), 45 (19.0), 44 (38.1), 43 (20.6), 42 (14.4), 41 (60.2), 40 (22.7), 39 (139), 38 (27.2), 32 (4.1), 31 (10.3), 30 (25.8); nmr (100 MHz, dimethyl sulfoxide-d_6) δ 11.54[27] (s, 0.86), 8.85 (s), 8.46 (s), 8.78 (s, 2.00, combined with area of absorption at δ 8.85 and 8.46), 7.66 (t), 7.47 (t), 7.25 (m, 5.93, combined with area of absorption at δ 7.66, 7.47), 5.22 (m, 0.92), 4.96 (s), 4.91 (s, 2.16, combined with absorption at δ 4.96), 2.75 (m, 2.14); nmr (100 MHz, pyridine-d_5) δ 13.0 (broad), 9.01 (s, 0.83), 8.54 (s, 0.17), 10.2 (s, 0.96), 8.49 (t, 0.16), 7.97 (t, 0.86), 7.74 (s, 5.04), 5.67 (m, 1.00), 5.03 (quartet, 1.92), 3.09 (m, 2.05); nmr (60 MHz, acetic acid-d_4) δ 11.4[28] (s), 8.82 (s), 8.50 (s), 8.45 (t), 7.67 (t), 7.28 (s), 5.43 (m), 4.98 (s), 2.82 (m).

(27) Exchanges upon addition of deuterium oxide.

(28) Time-averaged absorption due to rapid chemical exchange with the solvent.

Catalytic Hydrogenation of N-[(5-Hydroperoxy-2-oxo-3-pyrrolidinylidene)methyl]-N-Methylformamide (2a). (a) Over Platinum Oxide. Preparation of N-[(5-Hydroxy-2-oxo-3-pyrrolidinylidene)methyl]-N-methylformamide (3).—The hydroperoxide 2a (0.370 g, 2.00 mmol) in 175 ml of absolute ethanol was hydrogenated over platinum oxide catalyst (0.0110 g) at ambient pressure and temperature. Hydrogen uptake was rapid and complete in less than 90 min. A total of 2.2 mmol corresponding to 1.1 equiv of hydrogen was absorbed.

The catalyst was removed by filtration and the solvent was flash evaporated to yield a white solid, mp 180–200° dec. Recrystallization from absolute ethanol, filtration, and overnight drying at room temperature gave white crystals (0.260 g, 78%). A second recrystallization gave a sample: mp 200–205° dec (uncor) (turns slightly yellow above 150°); uv max (95% ethanol) λ_{max} 264 mμ (ϵ 21,200); ir (KBr disk) 3425 (OH), 3275 (OH), 3173 (NH), 3075 (NH), 1706 (HC=O), 1672 (pyrrolidone C=O), 1620 (C=C), 1451 (m) cm^{-1}; mass spectrum (70 eV, direct inlet, 100°) *m/e* (relative intensity) 152 (57.4), 142 (6.9), 141 (18.5), 140 (19.9), 124 (100); nmr (100 MHz, dimethyl sulfoxide-d_6), 8.59 (s, 0.64), 8.18 (s, 0.32), 8.38[27] (b, 1.00), 7.55 (t, 0.29), 7.31 (t, 0.77), 5.86 (d, 0.93), 5.13 (m, 0.99), 3.28 (s), 3.13 (s), 3.06 (m, 5.09, combined with area of absorption at δ 3.28 and 3.13); nmr (60 MHz, D_2O) 8.55 (s, 0.73), 8.22 (s, 0.34), 7.65 (t, 0.34), 7.36 (t, 0.73), 5.45 (four-line multiplet, 0.97), 3.68–2.80 (m, 5.13).

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.45; H, 6.03; N, 16.27.

(b) Over 5% Palladium on Charcoal. N-[(5-Hydroxy-2-oxo-3-pyrrolidinyl)methyl]-N-Methylformamide.—The hydroperoxide (0.931 g, 5.00 mmol) in 425 ml of absolute ethanol was hydrogenated over 5% palladium on powdered charcoal (0.186 g, 20% of starting material by weight) at atmospheric pressure and room temperature. Hydrogen uptake was very fast for 10 min, slower but constant to 90 min, and complete after 110 min. A total of 8.6 mmol corresponding to 1.7 equiv of hydrogen was taken up (86%). The catalyst was removed by filtration and the solvent was flash evaporated to yield a colorless oil which solidified on standing. Recrystallization from ethanol–ether, filtration, and vacuum drying at room temperature gave 0.690 g (74%) of white crystals: mp 142–143° (uncor); ir (KBr) 3400 (m), (broad), 3200 (s), 2800 (w), 2725 (w), 1684 (s), 1647 (s), 1454 (m) cm^{-1}; mass spectrum (70 eV, direct inlet, ambient temperature) *m/e* (relative intensity) 172 (1.3), 154 (9.4), 144 (6.4), 126 (38.5), 84 (23.2), 72 (100), 71 (4.3); nmr (60 MHz, 4:1 dimethyl sulfoxide-d_6–chloroform-*d*) δ 8.21[27] (b, 1.92, combined with area of absorption at δ 8.06), 8.06 (s), 5.75 (m, 0.97), 5.16 (m, 1.24), 3.50 (m, 1.94), 2.95 (s), 2.80 (s), 2.9 to 1.51 (m, 6.06, combined with area of absorption at δ 2.95, 2.80).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.02; N, 16.27. Found: C, 49.01; H, 7.06; N, 16.09.

N-Benzyl-N-[(5-Hydroxy-2-oxo-3-pyrrolidinylidene)methyl]-formamide.—A solution of the hydroperoxide 2b (0.393 g, 15.0 mmol) in 85 ml of absolute ethanol was hydrogenated over platinum oxide (0.0188 g) at atmospheric pressure and room temperature. The catalyst was removed by filtration and the solvent was evaporated to give a solid. Recrystallization from 25 ml of absolute ethanol gave 0.283 g (77%) of white solid. A second recrystallization from ethanol gave a sample: mp 168–170° dec (turns slightly yellow above 155°); uv max (ethanol) 263 mμ (ϵ 18,500); ir (KBr) 3475 (OH), 3330 (OH), 3185 (NH), 3050 (NH), 3023 (w), 1726 (HC=O), 1685 (pyrrolidone C=O), 1644 (C=C) cm^{-1}; nmr (60 MHz, dimethyl sulfoxide-d_6) δ 8.86 (s, 0.87), 8.45 (s, 0.16), 8.37 (broad, 0.85), 7.67 (t), 7.45 (t), 7.27 (m, 6.4, integrated with absorption at δ 7.67, 7.45), 5.78 (d, 0.97), 5.04 (m), 4.89 (s, 3.03, integrated with absorption at δ 5.04), 2.70 (m, 1.78); nmr (pyridine-d_5) δ 8.95 (s, 0.86), 8.66 (s, 0.19), 9.40 (broad, 0.93), 8.35 (t, 0.18), 7.85 (t, 0.88), 7.23 (s, 5.14), 5.48 (m, 1.02), 4.99 (s, 1.87), 3.00 (m, 1.91); mass spectrum (70 eV, direct inlet, 100°) *m/e* (relative intensity) 246 (2.5), 228 (13.8), 218 (10.3), 200 (100), 91 (96.2), 65 (56.0), 39 (25.3).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.22; H, 5.84; N, 11.35.

N-Benzyl-N-[(5-hydroxy-2-oxo-3-pyrrolidinyl)methyl]formamide.—A solution of hydroperoxide 2b (0.393 g, 1.50 mmol) in 175 ml of absolute ethanol was added to a slurry of prereduced 5% palladium on powdered charcoal (0.0786 g) in 10 ml of absolute ethanol. The mixture was hydrogenated at atmospheric

pressure and room temperature. Hydrogen uptake was very rapid for 15 min and then slow for 6 hr. A total of 1.9 equiv of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate flash evaporated to yield a pale yellow oil which did not crystallize on vacuum drying or on attempted crystallization from ethanol–ether or chloroform solution: ir (KBr) 3420 (s, shoulder), 3320 (s, b), 3070 (w, shoulder), 2790 (w), 1705 (s), 1665 (s), 1440 (m) cm^{-1}; ir (chloroform solution), 3420 (m), 3350 (m), 1705 (s), and 1660 (s) cm^{-1}; nmr (60 MHz, chloroform-*d*), δ 8.28 (s), 8.22 (s, 0.74, combined with absorption at δ 8.28), 7.67 (broad, 0.97), 7.3 (broad), 7.29 (s, 6.01, integrated with the absorption at δ 7.3), 4.52 (s), 4.47 (s, 2.08, integrated with absorption at δ 4.52), 3.51 (m, 2.11), 2.9–1.5 (two multiplets, 2.86).

N-Methyl-N-[(5-oxo-2-pyrrolin-4-ylidene)methyl]formamide (4).—Acetic anhydride (1.9 ml, 20.0 mmol) was added to a slurry of the unsaturated alcohol (0.340 g, 2.00 mmol) in 12.0 ml of anhydrous pyridine (distilled from molecular sieves 4A powder) in a 25-ml erlenmeyer flask. The flask was stoppered and the mixture was stirred magnetically at room temperature. The slurry became red upon mixing and very dark after several hours. Reaction progress was followed by tlc on Eastman silica gel strips (sheet 6060). After 16 hr, the slurry was cooled to −20° and filtered to give a dark solid which was washed with ethanol and vacuum dried to give 0.155 g of yellow solid. The filtrate was distilled to dryness (*ca.* 1 mm) at room temperature to give a black residue. Addition of a few milliliters of water and filtration gave an additional 16 mg of yellow solid. The total yield of dried product was 0.171 g (56%). Another reaction gave an 80% yield. Two recrystallizations from 95% ethanol gave a sample: mp 227–230° dec (uncor); uv max (95% ethanol) 263 mμ (ϵ 17,400), 361 (7500), (methanolic HCl) 266, 327 mμ; ir (KBr) 3120 (NH), 3060 (NH), 1700 (HC=O), 1673 (pyrrolidone C=O), 1582 (C=C), 1545 (C=C), cm^{-1}; mass spectrum (70 eV, direct inlet, 150°) *m/e* (relative intensity) 152 (21.9), 124 (100), 94 (18.7), 81 (45.3); nmr (100 MHz, dimethyl sulfoxide-d_6) δ 9.55[27] (b, 0.94), 8.77 (s, 0.76), 8.33 (s, 0.10), 7.69 (d, 0.07), 7.52 (d, 0.85), 6.69 (m, 1.10), 5.99 (d, 1.01), 3.35 (s), 3.23 (s).

Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.30; H, 5.25; N, 18.48.

N-Methyl-N-[(2-oxo-3-pyrrolidinyl)methyl]formamide (5).—A slurry of the diene 4 (0.304 g, 2.00 mmol) in 130 ml of 95% ethanol was hydrogenated over 5% palladium on powdered charcoal (0.0761 g) at atmospheric pressure and room temperature. Hydrogen uptake was very fast and complete in 30 min. A total of 4.01 mmol corresponding to 2.00 equiv of hydrogen was taken up. A plot of volume of hydrogen *vs.* time for the reaction showed no clean break in the resulting curve. The catalyst was removed by filtration and the solvent was flash evaporated to a colorless oil which turned yellow on standing. The oil was taken up in chloroform, applied to a 22 × 30 mm column of Florisil, and eluted with methanol. The methanol was removed by flash evaporation, and the resulting oil partially solidified on standing and was recrystallized from ethanol–ether to give 0.206 g (66%) of yellow, granular solid, mp 73–75°. Two further recrystallizations gave a sample: mp 78.5–80°; ir (KBr) 3200 (NH), 3075 (NH), 1705 (pyrrolidone C=O), 1660 (HC=O), 1450 (NH) cm^{-1}; mass spectrum (20 eV, direct inlet, 120°) *m/e* (relative intensity) 156 (2.8), 141 (0.2), 129 (7.4), 128 (100), 127 (7.5), 126 (4.8), 113 (1.7), 105.0, 99 (4.3), 98 (18.4), 86 (4.1), 85 (74.9), 84 (19.1), 75.0, 72 (8.4), 56.4, 44 (52.6), 30 (1.8), 26.9, 20.0, 19.8, 15.1; nmr (100 MHz, chloroform-*d*) δ 8.08 (s), 8.07 (s, 1.00, integrated with absorption at δ 8.08), 7.25[27] (d, 0.86), 3.58 (m), 3.37 (m, 4.18, integrated with absorption at δ 3.58), 2.99 (s), 2.89 (s, 2.92, integrated with absorption at δ 2.99), 2.65 (m, 1.25), 2.05 (m, 1.82).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 54.01; H, 7.63; N, 17.87.

N-Methyl-N-[(2-oxo-3-pyrrolidinylidene)methyl]formamide (4a).—A slurry of diene 4 (0.228 g, 1.50 mmol) in 100 ml of 95% ethanol was hydrogenated over platinum oxide (0.228 g) at atmospheric pressure and room temperature. Hydrogen uptake was moderate but stopped abruptly after 15 min. Only 0.32 equiv of hydrogen had been taken up. Since all of the diene had dissolved, the catalyst was removed by filtration. A fresh portion of platinum oxide (0.045 g) was added and the hydrogenation resumed. In 25 min, an additional 0.65 equiv of hydrogen was taken up (97% of theory) and uptake stopped. The catalyst was removed by filtration and the filtrate was flash evaporated to give a white solid. The solid was recrystallized from absolute ethanol–ether (*ca.* 1:2) and vacuum dried at room temperature to give 0.098 g (43%) of tan solid. A second recrystallization from ethanol–ether with the aid of activated charcoal gave white needles: mp 173.5–175.5° dec; uv max (95% ethanol) 264 mμ (ϵ 20,700); nmr (100 MHz, dimethyl sulfoxide-d_6) δ 8.62 (s, 0.71), 8.21 (s, 0.24), 7.83 (broad, 0.94), 7.54 (t, 0.27), 7.28 (t, 0.80), 3.34 (m), 3.33 (s), 3.18 (s), 3.10 (m, 7.06, integrated with absorption at δ 3.34, 3.33, 3.18); mass spectrum (70 eV, direct inlet, ambient temperature) *m/e* (relative intensity) 154 (11.9), 126 (100), 97 (38.0), 69 (55.7), 68 (69.8), 42 (43.1); ir (KBr), 3170 (NH), 3085 (NH), 1708 (HC=O), 1695 (pyrrolidone C=O), 1630 (C=C), 1458 (NH) cm^{-1}.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.72; H, 6.52; N, 18.21.

N-Methyl-N-[(1-methyl-2-oxo-3-pyrrolidinyl)methyl]formamide (6).—Mineral oil was removed from sodium hydride (93 mg, 56.8% dispersion in mineral oil, 2.2 mmol) (Metal Hydrides, Inc.) by addition and decantation of three 2-ml portions of dry dimethylformamide (distilled from calcium hydride). The washed sodium hydride was transferred to a 25-ml, round-bottomed, three-necked flask (dried in an oven and cooled in an atmosphere of dry nitrogen) with the aid of 2 ml of dry dimethylformamide. The slurry was stirred under dry nitrogen at room temperature while a solution of N-methyl-N-[(2-oxo-3-pyrrolidinyl)methyl]formamide (5) in 3 ml of dry dimethylformamide was added dropwise through a serum cap over a 15-min period. Gas evolution was observed. Addition of 2 ml of dry benzene (distilled and stored over sodium) to the slurry caused all the solid material to dissolve, resulting in a yellow solution which was stirred at room temperature for 1.25 hr. Dropwise addition of methyl iodide (0.137 ml, 2.2 mmol) (Eastman) to the solution over a 2-min period caused the temperature of the reaction mixture to rise slightly. The flask and contents were cooled in a bath of cool water, a gelatinous precipitate formed, and the mixture was stirred for 2 hr longer at room temperature before an additional portion of methyl iodide (0.137 mmol, 2.2 mmol) was added. Stirring was continued overnight under a nitrogen atmosphere.

Water (1 ml) was added to the reaction mixture and the solid material dissolved. More water (3 ml) and benzene (2 ml) were added until layers formed. The benzene layer was removed and the solution was extracted with three 1-ml portions of benzene and five 1-ml portions of chloroform. The combined extracts were dried over 2 g of crushed Drierite, filtered, and concentrated by flash evaporation to *ca.* 10–15 ml. The remaining solvent (mainly dimethylformamide) was distilled above 0.5 mm with the aid of a warm water bath to give a light orange oil (6). Tlc of the oil on Eastman silica gel 6060 strips in methanol gave a single spot at R_f 0.66. An nmr spectrum of the oil revealed that the sample contained a small amount of stopcock grease (Apiezon L) impurity; ir (liquid between NaCl disks) 2915 (m), 2880 (m), 1680 (s), 1495 (m), 1430 (m), 1390 (s), 1295 (m), 1255 (m), 1225 (w), 1115 (w), 1090 (m), 1075 (m), 1008 (w), 950 (w), 795 (w), 728 (w), and 710 (w) cm^{-1}; ir (CCl_4 solution) 2920 (m), 2848 (m), 1684 (s), 1495 (w), 1429 (w), 1402 (m), 1381 (m), 1292 (m), 1255 (m), 1212 (w), and 1070 (m) cm^{-1}; nmr (chloroform-*d*, 60 MHz) δ 8.11 (s, 0.99), 3.46 (m, 4.20), 3.00 (s), 2.88 (s), 2.63 (m, 6.91, integrated with absorptions at δ 3.00 and 2.88), 2.00 (m, 1.90); mass spectrum (20 eV, indirect inlet, *ca.* 100°) *m/e* (relative intensity) 172 (1.0), 171 (6.2), 170 (47.6), 155 (0.5), 143 (5.1), 142 (60.4), 141.3, 141 (16.8), 140 (8.5), 127 (3.1), 118.6, 115.3, 113 (8.1), 112 (43.2), 111 (17.1), 110 (11.3), 99 (100), 98 (97.5), 97.0, 88.3, 84 (10.5), 72 (17.5), 70 (6.2), 69.0, 44 (47.8), 42 (4.4).

3-Hydroxymethylene-1-methyl-2-pyrrolidinone (7).—Formylation of 1-methyl-2-pyrrolidinone (Eastman) was done according to the procedure of Korte and Büchel.[19] Purified potassium[29] (41.0 g, 1.00 mol) under dry toluene (600 ml) (dried over calcium chloride and then fresh potassium) was powdered by vigorously shaking the heated mixture. After being cooled to room temperature, the slurry was poured into a 2-l., 3-necked, round-bottomed flask equipped with a mechanical stirrer, water condenser, and addition funnel. The toluene was pipetted off and replaced with 200 ml of dry ether (distilled from lithium aluminum hydride). The suspension was stirred and cooled in

(29) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc. N. Y., 1967, p 905.

an ice bath as a mixture of 1-methyl-2-pyrrolidinone (114 g, 1.14 mol) (Eastman, practical) (distilled from calcium hydride) and ethyl formate (114 g, 1.50 mol) (dried over potassium carbonate and distilled from phosphorus pentoxide) in 100 ml of dry ether was added slowly (1.5 hr). During the addition, the reaction mixture turned red-brown and a salt precipitated. The ice bath was removed and the reaction mixture was stirred at room temperature. After 22 hr, the salt was filtered from the solution and stirred into 250 ml of 5 *M* hydrochloric acid (1.5 mol) with cooling. The acidified solution was filtered from inorganic salts and extracted with chloroform until the aqueous phase gave only a very slight enol reaction with ferric chloride (16 50-ml extractions). The chloroform extracts were dried overnight over Drierite and filtered; the chloroform was flash evaporated to give a yellow liquid. The concentrated extracts were fractionally distilled under reduced pressure. Chloroform was collected below room temperature (0.1 mm); a large amount of unreacted 1-methyl-2-pyrrolidinone was collected at 40–48° (0.1 mm); and a third constant boiling fraction was collected at 88° (0.1 mm). The third fraction distilled as a yellow oil which solidified on standing for a few minutes at room temperature. A large amount of charred material did not distil. The solid product was broken up and thoroughly washed with cold ether by suction filtration. Vacuum drying at room temperature for 4 hr gave 4.56 g (3.6%) of a yellow solid, mp 90–100°, and a small amount of the solid was recrystallized from acetone–petroleum ether (30–60°), mp 96–100° (lit.[19] mp 98°). The hydroxymethylene compound in water gave an intense green-blue color with 5% ferric chloride and a green color with cupric acetate. It had the following spectral properties: uv max (95% ethanol) 242 mμ (lit.[19] 241 mμ, log ε 4.17); ir (KBr) 2675 (broad, chelated OH), 1695 (C=O), 1635 (C=C) cm^{-1}; nmr (dimethyl sulfoxide-d_6, 60 MHz) δ 9.72 (s, OH or CHO), 7.13 (broad, OH or CHO), 3.33 (t, α-CH_2), 2.76 (s, CH_3), 2.55 (complex, β-CH_2 or methine proton), 3.7–1.9 (complex and broad, β-CH_2 or methine proton); mass spectrum (70 eV, indirect inlet) *m/e* (relative intensity) 127 (36.6), 126 (9.2), 99 (100), 98 (96.6).

1-Methyl-3-[(methylamino)methylene]-2-pyrrolidinone (8).—A solution of methylamine (18 ml, 0.40 mol) in 50 ml of cold, absolute ethanol was poured into a stirred solution of 3-hydroxymethylene-1-methyl-2-pyrrolidinone (**7**, 1.27 g, 0.010 mol) in 25 ml of absolute ethanol. The flask was protected by a drying tube and left at room temperature overnight. The solution was flash evaporated to a cream-colored solid which was taken up in hot methyl ethyl ketone and decolorized with activated charcoal. Addition of petroleum ether (bp 30–60°) to near the cloud point and refrigeration gave 0.926 g (66%) of light yellow solid: mp 134–138°; uv max (95% ethanol) 286 mμ (ε 26,000) (absorption completely disappears upon addition of a drop of dilute HCl); ir (KBr) 3263 (NH *trans*), 3155 (NH *cis*), 2912 (w), 2868 (w), 2846 (w), 2825 (w), 1674 (C=O), 1608 (C=C) cm^{-1}; ir (chloroform solution) 3420 (NH), 3340 (NH), 1690 (C=O), 1645 (C=C) cm^{-1}; nmr (chloroform-*d*, 60 MHz) δ 6.85[30a] (d, 0.73), 6.23[30a] (d, 0.15), 4.33[27] (b), 3.36 (t, 3.30, J = 7 Hz, integrated with absorption at δ 4.33), 2.86[30b] (m), 2.84 (s, 6.25, integrated with absorption at δ 2.86), 2.55 (t, 1.58, J = 7 Hz); mass spectrum (70 eV, indirect inlet, ambient temperature) *m/e* (relative intensity) 140 (100), 98 (40.8), 69 (53.0), 68 (64.3), 42 (46.5).

Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 60.04; H, 8.66; N, 19.86.

N-Methyl-N-[(1-methyl-2-oxo-3-pyrrolidinylidene)methyl]-formamide (9).—The formylation procedure described by Huffman was followed.[31] Acetic formic anhydride was prepared by heating acetic anhydride (0.378 ml, 4.00 mmol) and 98% formic acid (0.155 ml, 4.10 mmol) for 30 min at 56° (refluxing acetone bath) in a 5-ml round-bottomed flask equipped with a magnetic stir bar and a drying tube. The flask was transferred to a 26° water bath and 1-methyl-3-[(methylamino)methylene]-2-pyrrolidinone (**8**, 0.280 g, 2.00 mmol) was added to the stirred solution in small portions over a 5-min period. All of the solid dissolved. After 10 min, 2 ml of dry ether was added, resulting in precipitation of a cream-colored solid. The mixture was stirred at room temperature for 8.5 hr, filtered, washed with ether, and dried under vacuum for 1 hr at room temperature to give 0.186 g (55%) of tan solid, mp 150–152°. Refrigeration of the filtrate resulted in precipitation of an additional 37 mg of yellow solid bringing the yield to 66%. The product was recrystallized from absolute ethanol to give very fine white needles, mp 151.5–153°. A small sample was sublimed at 65–80° (0.25 mm) for microanalysis: uv max (95% ethanol) 267 mμ (ε 24,500); ir (KBr) 1702 (HC=O), 1671 (pyrrolidone C=O), 1624 (C=C) cm^{-1}; nmr (100 MHz, chloroform-*d*) δ 8.44 (s, 0.87), 8.07 (s, 0.10), 7.62 (t, 0.10), 7.27 (t, 0.92), 3.42 (m), 3.38 (s), 3.24 (s, 4.88, integrated with absorption at δ 3.42 and 3.38), 3.07 (m), 2.92 (s, 5.14, integrated with absorption at δ 3.07); mass spectrum (70 eV, direct inlet, ambient temperature) *m/e* (relative intensity) 168 (7.7), 140 (100), 116.7, 115.0, 109.0, 98 (23.2), 97 (21.2), 88.0, 69 (72.4), 68.6, 68 (69.2), 67.2, 67.0, 67 (9.7), 42 (64.6).

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.85; H, 7.31; N, 16.50.

Synthesis of N-Methyl-N-[(1-methyl-2-oxo-3-pyrrolidinyl)-methyl]formamide (6).—A solution of N-methyl-N-[(1-methyl-2-oxo-3-pyrrolidinylidene)methyl]formamide (**9**, 0.16 g, 1.00 mmol) in 25 ml of absolute ethanol was hydrogenated over 5% palladium on powdered charcoal (0.0336 g) at atmospheric pressure and room temperature. Hydrogen uptake was smooth and stopped after 30 min when 0.86 equiv of hydrogen had been taken up. The catalyst was removed by filtration and the solvent was flash evaporated at 40° to give a colorless oil. The oil was taken up in ether, filtered, and refrigerated, but crystallization did not occur. Tlc of this solution on an Eastman silica gel 6060 prepared sheet in methanol gave a single spot at R_f 0.66 upon visualization with molecular iodine. The solvent was evaporated in a stream of nitrogen and the oil dried overnight under vacuum at room temperature: ir (liquid between disks, CCl_4 solution) identical with that of saturated methyl pyrrolidinone **6** obtained by methylation of **5**; nmr (60 MHz, chloroform-*d*) identical with that of saturated methyl pyrrolidinone **6** obtained by methylation of **5**; mass spectrum (20 eV, indirect inlet, 120°) *m/e* (relative intensity) 172 (0.5), 171 (4.7), 170 (11.7), 155 (0.2), 142 (37.2), 141.3, 141 (6.3), 140 (5.1), 127 (1.2), 118.6, 112 (22.4), 111 (7.1), 110 (4.9), 100 (6.4), 99 (100), 98 (43.0), 97.0, 88.3, 84, 72 (7.6), 69.0, 44 (29.6), 42 (2.0), 15 (0.1).

Samples of saturated methylpyrrolidinone **6** prepared by hydrogenation of **9** and by methylation of **5** were mixed together in chloroform solution. Tlc of this mixture on Eastman silica gel 6060 strips gave only one spot (solvent, R_f): ether, 0.05; chloroform, 0.12; methanol, 0.66 (development with iodine).

Reaction of N-Benzyl-N-[(5-Hydroperoxy-2-oxo-3-pyrrolidinylidene)methyl]formamide with Ethanol in Dimethyl Sulfoxide.—Absolute ethanol was added to a solution of hydroperoxide **2b** (75 mg, 0.3 mmol) in 0.5 ml of dimethyl sulfoxide-d_6. The solution was heated on a steam bath and concentrated by passing a stream of dry air over it. Alternate addition of ethanol and evaporation of solvent was repeated several times until crystals deposited from the concentrated solution. The mixture was refrigerated and filtered to give a yellow solid. Two recrystallizations from absolute ethanol gave white needles: mp 147–150° dec; uv max (ethanol) 264 mμ; ir (KBr) 3330 (NH), 3078 (NH), 1715 (HC=O), 1681 (pyrrolidone C=O), 1637 (C=C) cm^{-1}; mass spectrum (70 eV, direct inlet, 100°) *m/e* (relative intensity) 246 (2.2), 229 (2.3), 228 (10.5), 200 (100), 109 (3.9), 106 (3.1), 91 (184), 65 (18.0), 39 (5.3); nmr (100 MHz, chloroform-*d*) 8.69, (s, 0.80), 8.27 (s, 0.10), 8.07 (b, 0.75), 7.61 (t, 0.15), 7.45 (t, 0.90), 7.17 (m, 5.06), 4.90 (m, 3.11), 3.68 (m), 3.34 (m, 2.20, integrated with absorption at δ 3.68), 2.77 (m, 1.91), 1.30 (m), 1.19 (m, 3.00, integrated with absorption at δ 1.30).

Reaction of 1-Benzyl-3-acetylpyridinium Chloride with Hydrogen Peroxide and Sodium Bicarbonate.—Treatment of 1-benzyl-3-acetylpyridinium chloride (12.4 g, 50.0 mmol) with 30% hydrogen peroxide (15.2 ml, 148 mmol) and sodium bicarbonate (4.20 g, 50.0 mmol) in water (50 ml) gave an orange solution, pH 9. The pH was 6.0 after 12 hr at 0–5° and an orange oil had formed. After 9 days, the solution had a pH of 5.0. The solution was decanted from the oil which was rinsed several times with water, taken up in a minimum amount of chloroform, and applied to a 27 × 2 cm column of dry-packed Florisil (100–200 mesh). A bright yellow oil was eluted with 1:1 hexane–ether; a white solid was eluted with 1:2 hexane–ether; a pale yellow oil was eluted with ether. Elution with chloroform and finally

(30) (a) Collapses to a singlet upon addition of D_2O. (b) Changes multiplicity upon addition of D_2O.

(31) C. W. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

with ethanol gave no other compounds, although dark-colored bands could be seen on the column.

The white solid was identified as N-benzylformamide, mp 59.5–60.5° (lit.[32] mp 60–61°). Its nmr spectrum was identical with that reported previously.[33]

Reaction of 1-Benzyl-3-bromopyridinium Chloride with Hydrogen Peroxide and Sodium Bicarbonate.—Treatment of 1-benzyl-3-bromopyridinium chloride (14.2 g, 50.0 mmol) with 30% hydrogen peroxide (15.2 ml, 148 mmol) and sodium bicarbonate (4.20 g, 50.0 mmol) in water (50 ml) yielded a yellow solution, pH 9.0. After 6 days at 0–5°, an oil had begun to form. The solution had a pH of 8.0 and effervescence was noted. The evolved gas was passed through a trap filled with saturated barium hydroxide solution. A white precipitate was formed immediately, indicating that the gas contained carbon dioxide. A control test with air was performed.

After 30 days the solution had a pH of 8.0 and was decanted from the yellow-orange oil that had formed. The oil was rinsed with water, taken up in 15 ml of chloroform (solution turned dark in color), and poured onto a 31 × 2 cm column of dry Florisil (100–200 mesh). Elution of the column with 2:1 hexane–ether gave a small amount of yellow oil which darkened on standing, a colorless fraction which was evaporated to give a white solid (2%), and a second yellow oil in very low yield. The white solid was identified as N-benzyl-2,2-dibromoacetamide. It was recrystallized several times from ethanol–water: mp 136.5–138° (uncor) and mmp (with an authentic sample[34]) 138–139° (uncor); ir (KBr disk) 3410 (w, broad), 3260 (m), 1648 (s) cm^{-1}; nmr (60 MHz, chloroform-*d*) δ 7.33 (C_6H_5, s, 5.09), 6.92 (NH, broad, 0.91), 5.86 ($CHBr_2$, s, 1.03), 4.46 (CH_2, d, 1.98, J_{CH-NH} = 6.0 Hz); mass spectrum (70 eV, indirect inlet, 25°) *m/e* (relative intensity) 227 (47.1), 225 (47.6), 146 (32.8), 104 (20.0), 103 (13.3), 91 (100.0).

Anal. Calcd for $C_9H_9NOBr_2$: C, 35.31; H, 2.95; N, 4.56; Br, 52.06; mol wt, 307. Found: C, 35.06, 35.25; H, 2.83, 2.99; N, 4.41, 4.66; N, 52.06; 51.86; mol wt, 313 (chloroform).

Registry No.—Hydrogen peroxide, 7722-84-1; 1-methyl-3-carbamoylpyridinium chloride, 1005-24-9; 1-benzyl-3-carbamoylpyridinium chloride, 5096-13-9; N-[(5-hydroxy-2-oxo-3-pyrrolidinyl)methyl]-N-methylformamide, 24744-90-9; N-benzyl-N-[(5-hydroxy-2-oxo-3-pyrrolidinylidene)methyl]formamide, 24744-91-0; N-benzyl-N-[(5-hydroxy-2-oxo-3-pyrrolidinyl)methyl]formamide, 24744-92-1; N-benzyl-2,2-dibromoacetamide, 24744-94-3; **2a**, 24744-81-8; **2b**, 24744-82-9; **3**, 24744-83-0; **4**, 24744-84-1; **4a**, 24744-85-2; **5**, 24744-86-3; **6**, 24799-54-0; **7**, 24744-87-4; **8**, 24744-88-5; **9**, 24744-89-6; **13**, 24744-93-2.

(32) F. F. Blicke and C.-J. Lu, *J. Amer. Chem. Soc.*, **74**, 3933 (1952).
(33) C. Franconi, *Z. Elektrochem.*, **65**, 645 (1961).
(34) The authentic sample was prepared by treatment of dibromoacetyl chloride with benzylamine.

Pyrido[2′,1′:2,3]imidazo[5,1-*a*]isoquinolinium Cation[1]

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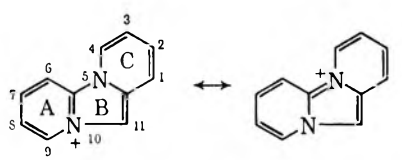
Received October 31, 1969

The first synthesis of the title cation has been effected *via* aromatic cyclodehydration of appropriately substituted 1-methylene-2-phenylimidazo[1,2-*a*]pyridinium bromides (**9** and **11**). The possibility that cyclization occurred in the pyrido ring (position 8) was excluded by showing that similar products (**3**) were obtained when position 8 was blocked with a methyl group.

Although the dipyrido[1,2-*a*:1′,2′-*c*]imidazolium cation (**1**)[2,3] and some of its benzologs[2,4,5] have been



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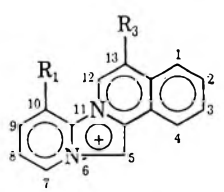
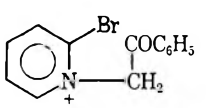
known for several years, the benzolog with the ring attached at positions 1 and 2 does not appear to have been reported. The synthesis of this benzolog, the pyrido[2′,1′:2,3]imidazo[5,1-*a*]isoquinolizinium cation (**2**) has now been accomplished.



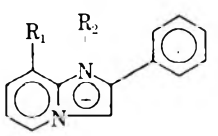
2, R_1 = H
3, R_1 = CH_3



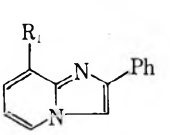
4

(1) This research was supported by Public Health Service Grant No. H-2170 of the National Heart Institute.
(2) B. R. Brown and J. Humphreys, *J. Chem. Soc.*, 2040 (1959).
(3) M. Hamana, B. Umezawa, and K. Noda, *Chem. Pharm. Bull.* (Tokyo), **11**, 694 (1963).
(4) B. R. Brown and E. H. Wild, *J. Chem. Soc.*, 1160 (1956).
(5) B. R. Brown and D. White, *ibid.*, 1589 (1957).

It has been shown[6] that, when certain amines are allowed to react with 2-bromo-1-phenacylpyridinium bromide (**4**), the product is a derivative of the 2-phenylimidazo[1,2-*a*]pyridinium ion (**5**). When the acetal of aminoacetaldehyde was allowed to react with the same quaternary salt (**4**), a product was obtained which was presumed to be impure 1-(2′,2′-diethoxyethyl)-2-phenylimidazo[1,2-*a*]pyridinium bromide (**6**). It would be expected that an acetal such as **6** would be hydrolyzed in hot mineral acid to the corresponding aldehyde (**9**, R_3 = H). In analogy to the behavior of 2-biphenylacetaldehyde[7] the resulting aldehyde would be expected



5, R_1 = H
6, R_1 = H; R_2 = $CH_2CH(OEt)_2$
9, R_1 = H; R_2 = CH_2COR_3
10, R_1 = H; R_2 = $CH{=}C(O^-){-}Ph$
11, R_1 = Me; R_2 = CH_2COR_3

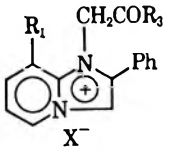


7, R_1 = H
8, R_1 = CH_3

(6) C. K. Bradsher, R. D. Brandau, J. E. Boliek, and T. L. Hough, *J. Org. Chem.*, **34**, 2129 (1969).
(7) C. K. Bradsher and W. J. Jackson, *J. Amer. Chem. Soc.*, **76**, 734 (1954).

TABLE I

FORMATION OF PYRIDOIMIDAZOLIUM SALTS



9, $R_1 = H$

11, $R_1 = CH_3$

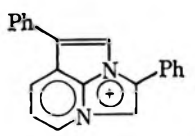
Compd no.	R_1	Mp of Br,[a] °C	Mp of ClO_4,[b] °C	Yield[c] of ClO_4, %	Uv max, mμ (log ε)
11	Ph	186–187[d]	206–208[e-g]	54	204.5 (4.71), 224.5 (4.48), 238 (4.50), 252 sh (4.39), 287 (4.32)
9	Me	205–207[f]	222–223[d,e,h]	64	204 (4.39), 222 sh (4.19), 284 (3.89)
11	Me	184–185[f]	175–176[i-k]	68	205 (4.41), 212 sh (4.36), 225 (4.29), 233 sh (4.26), 276 sh (4.01), 285 (4.06)
9	*t*-Bu	227–229[i]	211–212[e,i,l]	41	206 (4.20), 222 sh (4.00), 287.5 (3.88)

[a] The bromides, which tend to be hydrated, were used directly in the cyclization. [b] Mp of the analytical sample. Suitable analytical data were submitted, Ed. [c] This is the quaternization reaction when the salt is isolated as the perchlorate. [d] Needles. [e] From ethanol. [f] Powder. [g] Nmr (CF_3COOH) δ 6.20 (s, 2 CH_2), 2.73 (s, 3, CH_3). [h] Nmr (CF_3COOH) δ 5.45 (s, 2, CH_2), 2.37 (s, 3, CH_3). [i] Prisms. [j] From methanol. [k] Nmr (CF_3COOH) δ 5.61 (s, 2, CH_2), 2.73 (s, 3, $ArCH_3$), 2.37 (s, 3, CH_3CO). [l] Nmr (CF_3COOH) δ 5.57 [s, 2, CH_2), 1.15 (s, 9, $(CH_3)_3$].

to undergo aromatic cyclodehydration[8] to afford the pyrido[2′,1′:2,3]imidazo[5,1-*a*]isoquinolinium cation (**2**). In any case the product obtained by refluxing the acetal (**6**) in 48% hydrobromic acid was a pale yellow salt with no nonaromatic protons (below δ 7.18 in the nmr spectrum), and with a complex ultraviolet absorption spectrum characteristic of condensed polycyclic aromatic systems.

If this were the correct interpretation of our observations, it would follow that quaternization of 2-phenylimidazo[1,2-*a*]pyridine (**7**) at position 1 with an α-halomethyl ketone could provide intermediates (**9**) for the synthesis of homologs of the pyridoimidazoisoquinolinium cation (**2**) substituted at position 13. The 1-phenacyl-2-phenylimidazo[1,2-*a*]pyridinium ion (**9**, $R_3 = C_6H_5$) and the betaine (**10**) derived from it had been prepared by Tschitschibabin.[9] The betaine (**10**) in cold concentrated sulfuric acid gave a cyclization product (**2**, $R_3 = C_6H_5$) which from its ultraviolet absorption spectrum was easily recognizable as a derivative of **2**.

Whereas cyclization into the phenyl group rather than into the electron-deficient pyridine ring seemed attractive from a mechanistic viewpoint, it was necessary to exclude the possibility that the cyclization product was **12**.



12

Since 2-phenyl-8-methylimidazo[1,2-*a*]pyridine (**8**) was known,[10] it was easy to test whether cyclization would be blocked by a methyl group at position 8. The quaternization product (**11**, $R_3 = C_6H_5$; see also Table I) was cyclized to yield a cation which from the ultraviolet absorption spectrum (Table II) was very closely related in structure to the cyclization products obtained earlier (**2**, $R_3 = H$ and **2**, $R_3 = Ph$) and hence was not **12**.

By use of bromoacetone or 1-bromo-3,3-dimethyl-2-butanone as quaternizing agents, followed by cyclization of the resulting 2-phenylimidazo[1,2-*a*]pyridinium salts (Table I) the expected alkyl derivatives were obtained (Table II). The three alkyl derivatives of **2**, but not the 10-methyl-13-phenyl derivative (**3**, $R_3 = Ph$), crystallized with an additional 0.5 mol of perchloric acid/mol of salt. Other examples of this type of hydrogen bonding have been reported.[11] It is interesting that neither the parent compound nor the aryl derivatives exhibit this residual basicity which may depend upon the electron-release provided by the alkyl groups.

Experimental Section

All elemental analyses were by Janssen Pharmaceutica, Beerse, Belgium. The ultraviolet absorption spectra were determined in 95% ethanol solution using a Beckman DB-G spectrophotometer. The nmr data were obtained using tetramethylsilane as an internal standard when trifluoracetic acid was used as a solvent and as an external standard when deuterium oxide was the solvent.

Pyrido[2′,1′:2,3]imidazo[5,1-*a*]isoquinolinium Perchlorate (2).—To a solution of 3.7 g of 2-bromo-1-phenacylpyridinium bromide (**4**)[12] in 40 ml of absolute ethanol, 2.66 g of aminoacetaldehyde diethyl acetal was added, and, after the initial vigorous reaction, the mixture was refluxed for 1.5 hr. Removal of the solvent under reduced pressure left an oil which solidified on trituration with ethyl acetate, yield 3.0 g, mp 136–137°. Part of the crude solid (0.5 g) was refluxed for 16 hr in 10 ml of 48% hydrobromic acid although spectroscopic observations indicated that the reaction was essentially complete in 1.5 hr. Most of the hydrobromic acid was removed under reduced pressure, the residue dissolved in water, and 35% perchloric acid added. The precipitate was recrystallized from methanol. Additional data may be found in Table II.

2-Phenylpyrido[1,2-*a*]isoquino[2,1-*c*]imidazolium Perchlorate (2, R_3 = Ph).—The betaine (**10**)[9] of 1-phenacyl-2-phenylimidazo[1,2-*a*]pyridinium hydroxide (1.66 g) was dissolved in 10 ml of cold concentrated sulfuric acid and allowed to stand at room temperature for 6 hr. The solution was cooled in ice and then poured into 300 ml of cold anhydrous ether. The resulting precipitate was crystallized from methanol–ethyl acetate. Additional data may be found in Table II.

Reaction of Bromomethyl Ketones with 2-Phenylimidazo[1,2-*a*]pyridines (7 and 8).—Either 2-phenylimidazo[1,2-*a*]pyridine

(8) C. K. Bradsher, *Chem. Rev.*, **38**, 1946.

(9) A. E. Tschitschibabin, *Ber.*, **59**, 2045 (1926).

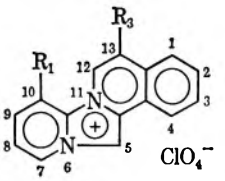
(10) F. Mattu and E. Marongin, *Ann. Chim.* (Rome), **54**, 495 (1964).

(11) *Cf.* H. F. Andrew and C. K. Bradsher, *J. Heterocycl. Chem.*, **3**, 282 (1966) and references cited therein.

(12) C. Djerassi and G. R. Pettit, *J. Amer. Chem. Soc.*, **76**, 4470 (1954).

TABLE II

PYRIDO[2′,1′:2,3]IMIDAZO[5,1-*a*]QUINOLINIUM PERCHLORATES



2 or 3

—Substituents— R1	R3	Compd no.	Cyclization— Time, hr	Temp, °C	Mp,[a] °C	Yield, %	λ_{max}, mμ (log ε)
H	H	6	16	126	241–243[b,c]	38[d]	208 (4.63), 243 (4.51), 255 (4.46), 263 (4.50), 275 (4.34), 290 (4.06), 302 (4.12), 338 (4.10), 354 (4.09), 370, (3.87)
H	Ph	10	6	20	208–210[e]	44[f]	206 (4.41), 243 (4.42), 259 (4.39), 266.5 (4.43), 291.5 (3.96), 303.5 (3.96), 340 (4.03), 358 (4.05), 373 (3.84)
Me	Ph	11[g]	6	20	245[b,h]	42	207 (4.30), 246 (4.42), 261 (4.37), 267.5 (4.38), 292.5 (3.76), 304 (3.81), 341 (4.10), 335 (4.12), 370 (4.00)
H	Me	9	4	100	262–264[i]	38	209.5 (4.34), 238.5 sh (4.44), 244.5 (4.52), 256.5 sh (4.42), 265 (4.49), 274 sh (4.38), 292 (3.97), 303 (3.95), 329 sh (3.97), 340 (4.08), 354 (4.03), 370 (3.95)
Me	Me	11	4	100	288[b,j]	42	210.5 (4.31), 239 sh (4.06), 246 (4.50), 264 (4.41), 276 sh (4.25), 291.5 (3.91), 304 (3.90), 349 (4.06), 364 (4.02), 383 (3.78)
H	*t*-Bu	9	8	100	188–189[k]	22	207.5 (4.43), 239 (4.33), 255 sh (4.17), 265 (4.25), 275 (4.20), 290 (4.06), 301 (4.03), 339 (3.80), 355 (3.69), 373 (3.54)

[a] Suitable analytical data were submitted, Ed. [b] With decomposition. [c] From methanol, light yellow needles. [d] Overall yield from 2-bromo-1-phenacylpyridinium bromide (**5**). [e] From MeOH–EtOAc, powder. [f] This is the yield of the bisulfate (mp 276° dec) which was converted to the perchlorate to afford an analytical sample. [g] The salt used for cyclization was the bromide. [h] From methanol, cream-colored powder, nmr (CF_3COOH) δ 3.22 (s, 3, CH_3). [i] From MeOH, cream-colored powder, nmr (D_2O) δ 2.08 (s, 3, CH_3). [j] From MeOH, light yellow needles, nmr (D_2O δ 2.70 (s, 3, CH_3), 2.17 (s, 3, CH_3). [k] From MeOH yellow prisms, nmr (CF_3COOH) δ 1.95 [s, 9, $(CH_3)_3$].

(**7**)[9] or the 8-methyl derivative (**8**)[10] was mixed with a molar equivalent of the bromomethyl ketone and the mixture heated on a steam bath for 8 hr (18 hr in the case of 1-bromo-3,3-dimethylbutanone[13]). The molten mass had usually become a thick green gum during the heating period. The gum was extracted with hot water; the extract was filtered, cooled, and extracted with several portions of ether. Finally the aqueous solution was charcoaled, filtered, and concentrated under reduced pressure, yielding the crude colorless salt. The crude bromide salt was once recrystallized from methanol–ethyl acetate or ethanol–ethyl acetate and the product (**9** or **11**) used for the cyclization experiment.

Since the bromide salts tended to be hygroscopic, a duplicate set of experiments was carried out in which the product was recovered as the perchlorate salt and the yields and analyses in Table I are of the perchlorate salts.

(13) M. Jackman, K. Klenk, B. Fishburn, B. F. Tullar, and S. Archer, *J. Amer. Chem. Soc.*, **70**, 2886 (1948).

Cyclization of Quaternary Salts (9 or 11).—The bromide salts (**9** or **11**, 0.005–0.0025 mol) were dissolved in 10 ml of concentrated sulfuric acid and after the proper interval at the appropriate temperature (Table II) the solution was worked up as in the preparation of 2-phenylpyrido[1′,2′:2,3]imidazo[5,1-*a*]isoquinolinium perchlorate (**3**, R_3 = C_6H_5). Further details may be found in Table II.

Registry No.—**1**, 245-75-0; **2** (R^3 = H), 25110-24-1; **2** (R^3 = Ph), 25110-25-2; **2** (R^3 = Me), 25110-26-3; **2** (R^3 = *t*-Bu), 25110-27-4; **3** (R^3 = Ph), 25110-28-5; **3** (R^3 = Me), 25158-28-5; **9** (R^3 = Me) bromide, 25110-29-6; **9** (R^3 = Me) perchlorate, 25110-30-9; **9** (R^3 = *t*-Bu) bromide, 25158-29-6; **9** (R^3 = *t*-Bu) perchlorate, 25110-31-0; **11** (R^3 = Ph) bromide, 25158-30-9; **11** (R^3 = Ph) perchlorate, 25110-32-1; **11** (R^3 = Me) bromide, 25110-33-2; **11** (R^3 = Me) perchlorate, 25110-34-3.

Bimolecular Reduction of Isoquinoline. Epimeric 1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinolines and Derivatives

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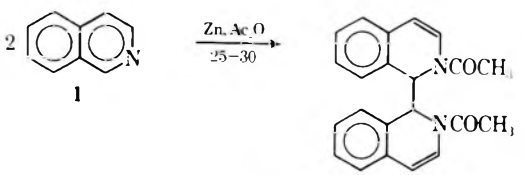
Bimolecular reduction of isoquinoline with zinc–acetic anhydride led to a 1:1 mixture of epimeric 2,2′-diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines, **2a,b** (54–58% total yield). Hydrogenation of **2a,b** with rhodium–charcoal catalyst in acetic acid gave, with retention of stereochemistry, epimeric 2,2′-diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinolines, **3a,b** (98% yield); these were hydrolyzed with aqueous hydrobromic acid–acetic acid to the corresponding 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline bishydrobromide salts, **4a,b**, which were converted to the title diamines, **5a,b**, on neutralization. Hydrolysis of *dl*-diamide **3a** in refluxing concentrated hydrobromic acid produced *dl*-8-methyl-5,6,7,9,10,11,15b,15c-octahydrodiisoquino[2,1-*c*:1′,2′-*e*]imidazolinium bromide, **7a**; hydrolysis of *meso*-diamide **3b** under the same conditions gave only bishydrobromide, **4b**. Imidazolinium bromide **7a** is stable in refluxing aqueous hydrobromic acid–acetic acid; in refluxing aqueous ethanolic sodium hydroxide it forms *dl*-2-acetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (**6a**). Reaction of diamines **5a,b** with formaldehyde led to epimeric 5,6,7,9,10,11,15b,15c-octahydro-8H-diisoquino[2,1-*c*:1′,2′-*e*]-imidazoles, **8a,b**; the stereochemistry of these compounds was established by interpretation of their nmr spectra. Hydrogenation of 1,1′-biisoquinoline bishydrochloride with platinum in ethanol led to *meso*-diamine, **5b**, exclusively. 1,1′-Biisoquinoline was produced by dehydrogenation of diamines **5a,b** with palladium–charcoal catalyst in refluxing *p*-cymene (65–70% yield). Hydrogenation of 1,1′-biisoquinoline with rhodium–charcoal catalyst in acetic acid gave 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-biisoquinoline (**13**). Reaction of diamides **2a,b** with N-bromosuccinimide in acetic acid led to epimeric 2,2′-diacetyl-1,1′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines, **18a,b**; in refluxing aqueous ethanolic sodium hydroxide, **18a,b** produce nearly equal amounts of isoquinoline and 1-bromoisoquinoline.

Bimolecular reduction of isoquinoline (**1**) under conditions of the Dimroth reaction (zinc–acetic anhydride)[1] has provided a convenient entry into the unsubstituted 1,1′-biisoquinoline ring system. Employing an improved procedure which had been applied to pyridine,[2] isoquinoline gave epimeric 2,2′-diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines (**2a,b**) in

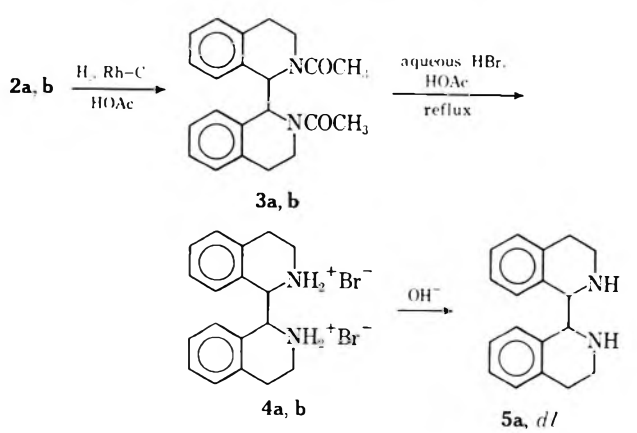


1

2a, *dl*
b, *meso*

54–58% total yield (*ca.* 1:1 ratio). In a previous study of the reaction with isoquinoline, Elliott and McGriff obtained epimer **2a** only (18% yield).[3] The very low solubility of **2b** in various solvents, relative to that of **2a**, facilitates separation of the epimer mixture. Stereochemistry of these compounds has been established.

2,2′-Diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline epimers **3a,b** were obtained in 98% yield by



3a, b

4a, b

5a, *dl*
b, *meso*

hydrogenation of the corresponding tetrahydro compounds **2a,b** with rhodium–charcoal catalyst in acetic acid solvent. Stereochemistry is retained in the reduction.

Amides **3a,b** are quite resistant to hydrolysis by acids and bases. Hydrolysis to the 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline bishydrobromide salts, **4a,b**, was effected in aqueous hydrobromic acid–acetic acid (48-hr reflux; 70–80% yield). The free diamines, **5a,b** were liberated quantitatively from their salts in aqueous methanolic sodium hydroxide–tetrahydrofuran solution.

Hydrolysis of diamides **3a,b** was incomplete in refluxing concentrated hydrobromic acid containing no added acetic acid. The two epimers behaved differently. *dl* epimer **3a** produced *dl*-8-methyl-5,6,7,9,-10,11,15b,15c-octahydrodiisoquino[2,1-*c*:1′,2′-*e*]imidazolinium bromide (**7a**). The *meso* epimer (**3b**) was hydrolyzed to diamine bishydrobromide salt **4b**.

Imidazolinium salt **7a** was hydrolyzed readily in refluxing aqueous ethanolic sodium hydroxide to produce monoamide **6a**; like diamides **3a,b**, amide **6a** is rather resistant to alkaline hydrolysis. Monoamide **6a** in refluxing concentrated hydrobromic acid regenerated **7a**, and in aqueous hydrobromic–acetic acid formed bishydrobromide salt **4a**. Monoamide **6a** is clearly an intermediate in these transformations originating from diamide **3a**; it reacted with acetic anhydride to regenerate **3a**. Salts of 1,2-diamine monoamides form imidazolinium salts on heating.[4]

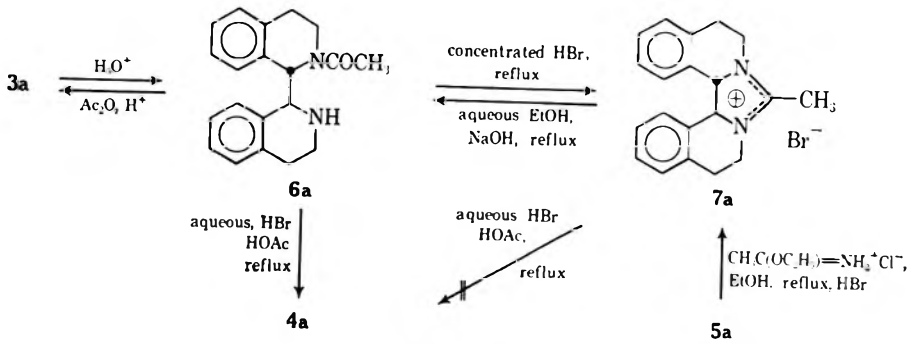
Hydrolysis of imidazolinium salt **7a** to bishydrobromide salt **4a** could *not* be effected in refluxing aqueous hydrobromic acid–acetic acid (48 hr). In view of the

(1) (a) O. Dimroth and R. Heene, *Chem. Ber.*, **54**, 2934 (1921); (b) O. Dimroth and F. Frister, *ibid.*, **55**, 1223 (1922).

(2) The product, 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine, is obtained in 45–47% yield. (a) A. T. Nielsen, D. W. Moore, G. M. Muha, and K. H. Berry, *J. Org. Chem.*, **29**, 2175 (1964). (b) A. T. Nielsen, D. W. Moore, J. H. Mazur, and K. H. Berry, *ibid.*, **29**, 2898 (1964).

(3) I. W. Elliott, Jr., and R. B. McGriff *J. Org. Chem.*, **22**, 514 (1957).

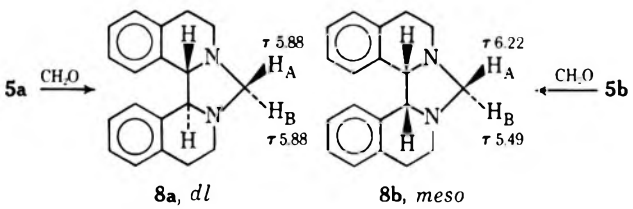
(4) E. Waldmann and A. Chwala, *Chem. Ber.*, **74**, 1763 (1941).



ease of formation of salt **4a** from monoamide **6a** in this medium, this finding indicates the rate of the **6a** → **4a** transformation to be very fast, relative to formation of imidazolinium salt **7a**, in this more dilute acid medium. The more strongly acidic concentrated hydrobromic acid favors the dehydration reaction involved in the **6a** hydrobromide → **7a** transformation over the **6a** → **4a** hydrolysis. Rehydration of **7a** to form **6a** evidently does not occur in dilute acid.

The structure and stereochemistry of imidazolinium salt **7a** was affirmed by an alternate synthesis. Reaction of *dl*-diamine **5a** with ethyl acetimidate hydrochloride in refluxing ethanol[5] led to the imidazolinium chloride salt (**7a**, Br = Cl), which could be converted to **7a** by treatment with excess hydrobromic acid. No imidazolinium salt could be prepared by reaction of *meso*-diamine **5b** with ethyl acetimidate hydrochloride, nor from *meso*-diamide **3b** in strongly acidic medium.

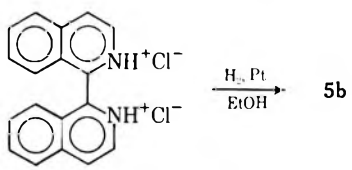
Ring closure to the more flexible imidazolidine ring could be realized with both diamine epimers, **5a,b**. Reaction with formaldehyde in dioxane at 90° led to the epimeric 5,6,7,9,10,11,15b,15c-octahydro-8H-diisoquino[2,1-*c*:1′,2′-*e*]imidazoles: 100% yield of **8a** from **5a**; 62% yield of **8b** from **5b**.



8a, *dl* **8b**, *meso*

The stereochemistry of imidazolidines **8a,b** is apparent from an examination of their nmr spectra. The signals exhibited by the C-8 methylene bridge hydrogens ($H_{A,B}$) of the imidazolidine ring establish the stereochemistry. In the *dl* epimer this signal is a single line at τ 5.88, since H_A and H_B are in a similar environment with respect to the lone-pair electrons of the adjacent nitrogens and the imidazolidine ring hydrogens at C-15b and C-15c, which appear as a singlet at τ 6.03. In the *meso* epimer **8b** the $H_{A,B}$ signals are split and appear as an AB quartet centered at τ 5.86 with bands at τ 6.22 and 5.49 (J = 7.7 Hz) assigned as shown in the formula. The imidazolidine ring hydrogens in **8b** appear as a single line at τ 5.32. The remainder of the spectrum in both epimers is similar and reveals aryl protons (8) at τ 2.6–3.3 and piperidine ring protons (8) at τ 6.7–7.5. Published investigations on the stereochemistry of *meso*- and *dl*-perhydropyrido[1.2-*c*:2′,1′-*e*]imidazoles,[6] and 15b,15c-dimethyl derivatives of **8a,b**,[7] reveal similar nmr spectra.

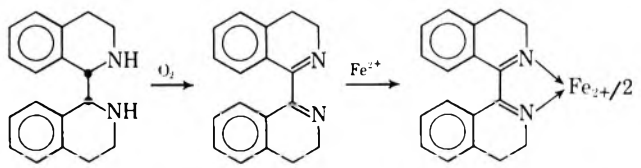
Diamine epimer **5b** was synthesized by an alternate route—hydrogenation of 1,1′-biisoquinoline dihydrochloride (**9**) in ethanol with platinum catalyst. Neither



9

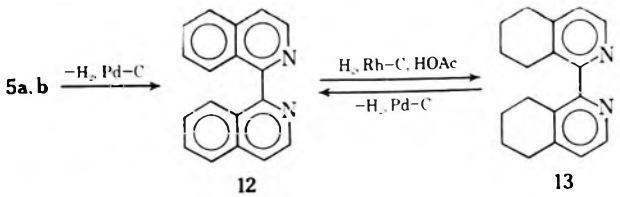
epimer **5a** nor any crystalline product other than **5b** was isolated as a product of this reduction. Methoxy derivatives of 1,1′-biisoquinoline hydrochloride have been hydrogenated under similar conditions to produce a single epimer of methoxy derivatives of **5** (stereochemistry unknown).[8]

Dimer epimer **5b** was found to decompose slowly to an oily yellow material when stored in air at room temperature for several weeks; the *dl*-diamine **5a** showed no evidence of decomposition when stored under these conditions. The decomposition reaction is evidently complex. Partially decomposed samples show ultraviolet absorption bands characteristic of isoquinoline and biisoquinoline (λ_{max}^{EtOH} 323 nm). They also react with ferrous salts to produce an intense blue color (λ_{max}^{EtOH} 550, 635, 656 nm) shown by iron(II) complex **11** of known 3,3′,4,4′-tetrahydro-1,1′-biisoquinoline (**10**).[9,10]



5b, *meso* **10** **11**, deep blue

Diamines **5a,b** were each readily dehydrogenated to 1,1′-biisoquinoline (**12**) by palladium–charcoal catalyst in boiling *p*-cymene (65–70% yield).



12 **13**

(5) C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, **69**, 1688 (1947).

(6) P. J. Chivers, T. A. Crabb, and R. O. Williams, *Tetrahedron*, **24**, 6625 (1968); **25**, 2921 (1969).

(7) P. Cerutti and H. Schmid, *Helv. Chim Acta*, **47**, 203 (1964).

(8) I. Matsuo and T. Takahashi, Japanese Patent 16551 (1965); *Chem. Abstr.*, **63**, 18,053 (1965).

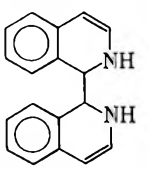
(9) R. A. Henry and C. Heller, forthcoming publication, this laboratory.

(10) I. Matsuo, T. Takahashi, and S. Ohki, *Yakugaku Zasshi*, **83**, 518 (1963); *Chem. Abstr.*, **59**, 7483 (1963).

Hydrogenation of 1,1′-biisoquinoline (**12**) in acetic acid with rhodium–charcoal catalyst produced neither diamine **5a** nor **5b**. Prolonged reaction (80–90 hr) at 25° resulted in hydrogenation of the carbocyclic rings, with formation of 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-biisoquinoline (**13**) as the sole crystalline product (*ca.* 34% yield).

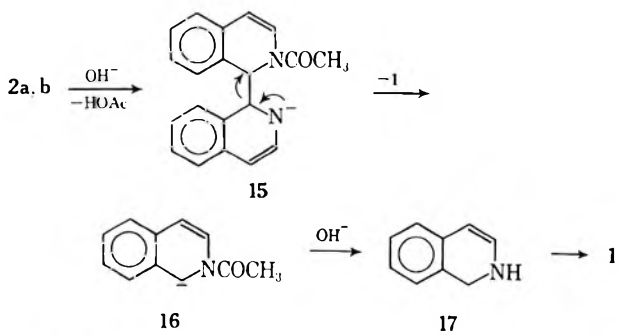
The structure of **13** follows from its nmr spectrum which shows the bipyridine ring protons as an AB quartet, with the C-3,3′ proton signal centered at τ 1.66 and the C-4,4′ signal at 3.03 (J = 6 Hz); the 6,6′,7,7′-ethylene protons (8) appear at 8.0–8.5 as a multiplet, the C-5,5′ methylene protons (4) as a multiplet centered at 7.55, and the C-8,8′ protons (4) as a multiplet centered at 7.22. The ultraviolet spectrum of **13** is equivalent to two independently absorbing alkyl-substituted pyridine rings rather than a coplanar 2,2′-bipyridine, owing to the noncoplanarity of the isoquinoline rings: λ_{max} 272 nm (ϵ_{max} 6200).[11] Dehydrogenation of **13** by heating with palladium–charcoal catalyst in boiling *p*-cymene led to 1,1′-biisoquinoline.

The 1,1′,2,2′-tetrahydro-1,1′-biisoquinoline epimers, **14a,b**, parents to diamides **2a,b**, could not be isolated. Diamides **2a,b** are converted principally to isoquinoline by acid or basic hydrolysis, and are rather resistant to acid hydrolysis.[3] Traces of 1,1′-biisoquinoline have been obtained by acid hydrolysis of **2a**.[3]

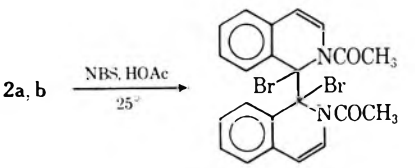


14a,b

Reaction of diamides **2a,b** with refluxing aqueous ethanolic sodium hydroxide (16 hr) produced isoquinoline in nearly quantitative yield. This facile base-catalyzed cleavage contrasts with the behavior of the corresponding octahydrodiamides, **3a,b**, and monoamide **6a**, which are quite stable under the same conditions. The results suggest ease of 1,1′-carbon-bond cleavage in the amide anion intermediate (**15**), leading to isoquinoline and anion intermediate **16**. Hydrolysis of protonated **16** (known, relatively stable 1-acetyl-1,2-dihydroisoquinoline)[12] leads to 1,2-dihydroisoquinoline, **17**. Unpolymerized, neat 1,2-dihydroisoquinoline is reported to disproportionate very rapidly to isoquinoline and 1,2,3,4-tetrahydroisoquinoline,[12] and oxygen oxidation of the latter provides 1,2-dihydroisoquinoline.[13] Thus 1,2-dihydroisoquinoline can be completely consumed in formation of isoquinoline.

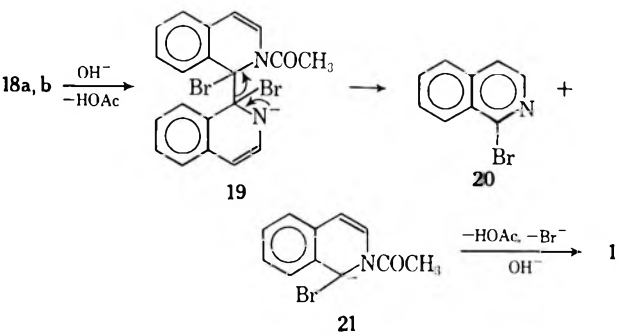


Reaction of diamides **2a,b** with N-bromosuccinimide in acetic acid led to 2,2′-diacetyl-1,1′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines (**18a,b**). Exclusive formation of a single epimer, in nearly quantitative yield, is observed in each case, probably with retention of stereochemistry (*e.g.*, *dl*-**2a** → *dl*-**18a**). A highly reactive radical intermediate would be involved in a stereoselective process.[14,15]



18a, b

Hydrolysis of both dibromo compounds (**18a,b**) in refluxing aqueous ethanolic sodium hydroxide led to a mixture of 1-bromoisoquinoline (**20**) and isoquinoline (**1**) in nearly equal amounts. Supposing an initial amide hydrolysis, amide ion intermediate **19** would cleave to (or a synchronous process would lead to) 1-bromoisoquinoline (**20**) and anion intermediate **21**. Hydrolysis of protonated **21** (2-acetyl-1-bromo-1,2-dihydroisoquinoline) would result in elimination of bromide ion with formation of isoquinoline.



Experimental Section

Melting points were determined on a Kofler block and are corrected. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer in 95% ethanol, infrared spectra on a Perkin-Elmer Model 137 spectrophotometer, and nmr spectra on a Varian A-60 spectrometer. Mass spectra were determined on a Hitachi Model RMU-6E, 80 eV. Magnesium sulfate was employed as drying agent. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

dl-**2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline** (**2a**). —Isoquinoline (270 g of 95% assay, mp 18–20°, 2.0 mol) was dissolved in 1500 ml of acetic anhydride. While stirring vigorously, maintaining a nitrogen atmosphere, zinc dust (300 g of CP, 99% assay) was added in small portions at regular intervals during 3 hr keeping the temperature of the reaction mixture at 30–35° by external ice bath cooling. Stirring was continued at 25–30° for 15 hr (nitrogen atmosphere). The pale yellow mixture was then poured into a large stainless steel beaker containing 4 l. of water and 4 l. of ice cubes. After a period of 7 hr most of the liquid was removed by decantation. The remaining material was filtered and the collected solid washed several times with

(11) Alkyl-substituted 2,2,-bipyridine derivatives not substituted in the 6 position have intense bands between 280 and 290 nm (ϵ_{max} 12,000–17,000): W. H. F. Sasse and C. P. Whittle, *J. Chem. Soc.*, 1347 (1961). Alkylpyridines have relatively weak bands near 270 nm (ϵ_{max} 2000–3000): C. T. Kyte, G. H. Jeffery, and A. I. Vogel, *ibid.*, 4454 (1960).

(12) W. P. Neumann, *Justus Liebigs Ann. Chem.*, **618**, 90 (1958).

(13) W. Bartok and H. Pobiner, *J. Org. Chem.*, **30**, 274 (1965).

(14) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Amer. Chem. Soc.*, **90**, 5793 (1968).

(15) C. W. Jefford and E. H. Yen, *Tetrahedron Lett.*, 4477 (1966).

water. The orange-yellow, granular solid was digested with 1300 ml of boiling methanol for 2 hr, filtered hot, and the solid washed with 500 ml of methanol. The filtrate was concentrated to a volume of *ca.* 500 ml and chilled at 0°; the crystals were collected and washed with ice-cold methanol to yield 82 g (24%) of **2a**, mp 185–196°. Recrystallization from methanol gave 64 g of large, colorless, chunky prisms, mp 194–195°, which changed to needles near the melting point and melted at 205–208°, lit.[3] mp 193–194°. Parallel runs gave 24–26% yields of high purity, uncrystallized **2a**. When the temperature during the addition was maintained above 30–35° (up to 60°), yields of **2a** decreased slightly and yields of **2b** increased; total yields remained approximately the same (54–58%). Spectra of **2a**: λ_{max} (EtOH) 207 nm (ϵ 27,000), 228 (28,100), 306 (14,500); lit.[3] 229 nm (15,800), 205 (10,200); ν_{KBr} 1670 cm^{-1} (C=O), 1620 (C=C); nmr ($CDCl_3$) τ 2.4–2.7 (m, 4, aryl), 2.8–3.2 (m, 4, aryl), 3.97 (s, 2, CH at C-1,1′), AB quartet at 3.60, 3.85 (J = 8 Hz, 4, CH=CH at C-3,3′,4,4′) 7.78 (s, 6, CH_3CO).

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13; mol wt, 344.4. Found: C, 76.87; H, 5.87; N, 8.27; mol wt, 333 (osmometry).

A 1.0-g sample of **2a**, 2.5 g of sodium hydroxide, 3 ml of water, and 15 ml of ethanol were heated on the steam bath for 16 hr. The solution was concentrated under reduced pressure and the residue extracted with methylene chloride. The dried extracts were concentrated to dryness to yield 0.77 g of a mobile oil, soluble in heptane, having the odor of isoquinoline; its infrared spectrum (film) was practically identical with that of isoquinoline (theoretical yield, 0.75 g).

meso-**2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (2b).**—The dried residue remaining after extraction with hot methanol in the preparation of **2a** described above is a mixture containing principally zinc and rather pure **2b** (white crystals, mp 250–251°). It was extracted continuously with 1200 ml of methylene chloride in a Soxhlet apparatus for 30 hr, leaving 184 g of zinc and depositing from solution 79.7 g of white, crystalline **2b**, mp 255–257°; concentration of the filtrate to dryness, followed by washing of the residue with water and ethanol, gave 23.6 g more of **2b**, mp 250–251°; total yield of **2b** was 103.3 g (30%); in parallel runs the yield was 28–32%. The compound is quite insoluble in all organic solvents tested. Recrystallization from boiling acetic acid (2% solution) yields rectangular prisms: mp 257–260°; λ_{max} (EtOH) 207 nm (ϵ 23,900), 241 (26,800), 315 (12,200); ν_{KBr} 1660 cm^{-1} (C=O), 1620 (C=C).

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.49; H, 6.01; N, 7.98.

A 3.44-g (0.01 mol) sample of **2b** and 25 ml each of concentrated hydrobromic acid, acetic acid and water were heated under reflux for 63 hr. The clear, pale yellow solution was concentrated in vacuum to remove solvents. One-half of the residue was dissolved in 10 ml of hot absolute ethanol and diluted with 100 ml of ether; an oil precipitated which failed to crystallize. One-half of the residue was dissolved in water (10 ml) and treated with saturated potassium carbonate solution to liberate an oil which was extracted with methylene chloride. Concentration of the extracts in vacuum gave 1.26 g of a viscous, dark red oil, not completely soluble in heptane, which had a strong odor of isoquinoline and an infrared spectrum similar to that of isoquinoline (C=O bands absent). Attempted crystallization of the oil from heptane–benzene gave a gum.

dl-**2,2′-Diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (3a).**—*dl*-2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (**2a**, 50.0 g), 200 ml of acetic acid, and 15.0 g of 5% rhodium–charcoal catalyst were shaken with hydrogen (25–55 psi) in a Parr apparatus at 25° until hydrogen uptake ceased (86 hr) and 2 mol equiv of hydrogen was absorbed. The mixture was filtered through a Büchner funnel and the catalyst extracted three times with hot acetic acid. The extracts and the filtrate were concentrated to dryness and the residue was triturated with water, filtered, and washed with water to yield 49.4 g (98%) of diamide **3a**, mp 204–210°. Recrystallization from benzene gave chunky white prisms: mp 211–213°; ν (KBr) 1645 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.7–3.5 (m, 6, aryl), 4.03 (d, 2, J = 8 Hz, CH at C-8,8′), 4.53 (s, 2, CH at C-1,1′), 6.0–7.5 (m, 8, CH_2CH_2 at C-3,3′,4,4′), 7.92 (s, 6, CH_3CO). Substitution of platinum oxide or palladium–charcoal catalysts for the rhodium–charcoal failed to hydrogenate **2a** which was recovered.

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04; mol wt, 348.43. Found: C, 76.05; H, 7.07; N, 7.98; mol wt, 332 (osmometry).

A solution of **3a** (0.50 g) and 1.0 g of sodium hydroxide in 10 ml of 50% aqueous ethanol was heated under reflux for 16 hr. The pale yellow solution was concentrated to dryness and the residue diluted with water to precipitate 0.49 g of recovered **3a**, mp 190–210°.

A solution of **3a** (0.50 g) in 5 ml of concentrated hydrobromic acid was heated on the steam bath (90°) for 18.5 hr. The solution was concentrated to dryness and the residue diluted with water to precipitate 0.47 g of recovered **3a**, mp 210–212°; when this was mixed with **3a** the melting point was not depressed.

meso-**2,2′-Diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (3b).**—*meso*-2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (**2b**, 50.0 g), 230 ml of acetic acid, and 15.0 g of 5% rhodium–charcoal catalyst were shaken with hydrogen as in the preparation of **3a**, above; 2 mol equiv of hydrogen were absorbed in 76 hr, after which time hydrogen uptake ceased. The insoluble product mixed with catalyst was filtered and extracted continuously with methylene chloride in a Soxhlet apparatus for 40 hr. The extract was concentrated to dryness and the residue triturated with water, filtered, and washed with water to yield 49.5 g (98%) of diamide **3b**, mp 231–233°. Recrystallization from benzene gave flat square prisms: mp 231–232°; ν (KBr) 1640 cm^{-1} (C=O). The nmr spectrum ($CDCl_3$) at *ca.* 30° revealed two acetyl and C-1,1′ proton signals due to the presence of two conformers (A, *ca.* 67% and B, *ca.* 33%); τ 2.3–3.6 (m, 8, aryl), 3.92 (s, CH at C-1,1′ of B), 4.08, 4.63 (AB quartet, J = 5 Hz, CH at C-1,1′ of A), 6.0–7.5 (m, 8, CH_2CH_2 at C-3,3′,4,4′), 7.90 (s, CH_3CO of A), 8.20 (s, CH_3CO of B).[16] In DMSO-d_6 the nmr spectrum at 40° is very similar to that in $CDCl_3$, but at 120° there resulted a collapse of the methyl signals to a single line; also, the signals for the C-1,1′ protons coalesce to a single broad signal.

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04; mol wt, 348.43. Found: C, 76.16; H, 6.84; N, 8.02; mol wt, 351 (osmometry).

dl-**1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline Bishydrobromide (4a).**—A mixture of *dl*-2,2′-diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline, **3a**, (34.8 g, 0.1 mol) and 250 ml each of concentrated hydrobromic acid, acetic acid, and water was heated under reflux for 48 hr. The clear, pale yellow solution was concentrated to dryness under reduced pressure. The residue was triturated with water, filtered, and washed with water to yield 32.2 g (75.5%) of salt **4a**, small prisms, mp 280–285°. Recrystallization from 0.8 *N* aqueous hydrobromic acid gave large chunky prisms: mp 290–292°; nmr (D_2O) τ 2.3–2.9 (m, 8, aryl), 4.18 (d, J = 1 Hz, CH at C-1,1′), 5.8–6.8 (m, 8, CH_2CH_2 at C-3,3′,4,4′). Parallel runs gave **4a** in 75–79% yield.

Anal. Calcd for $C_{18}H_{22}Br_2N_2$: C, 50.73; H, 5.20; N, 6.57; Br, 37.50. Found: C, 50.77; H, 5.17; N, 6.58; Br, 37.50.

meso-**1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline Bishydrobromide (4b).**—The procedure employed above with the *dl* isomer **3a** was applied to *dl*-2,2′-diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline, **3b** (34.8 g, 0.1 mol), to yield 30.3 g (71%) of salt **4b** as chunky prisms, mp 264–269°. Parallel runs gave **4b** in 71–80% yield.

Anal. Calcd for $C_{18}H_{22}Br_2N_2$: C, 50.73; H, 5.20; N, 6.57; Br, 37.50. Found: C, 50.93; H, 4.93; Br, 37.57.

dl-**1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline (5a).**—A 30.0-g sample of the *dl* bishydrobromide salt **4a** was dissolved in a solution of 100 ml each of 10% aqueous sodium hydroxide, methanol, and tetrahydrofuran by shaking at 25°. The clear solution was concentrated under reduced pressure on the steam bath to a volume of *ca.* 50 ml. The residue was filtered and the solid washed with water to yield 18.6 g (100%) of diamine **5a**, mp 134–138°. Recrystallization from 4:1 ethanol–water gave chunky prisms: 15.6 g; mp 135–137.5°; λ_{max} (EtOH), 259 nm (ϵ 955), 266.5 (1100), 273.5 (1100); nmr ($CDCl_3$) τ 2.5–3.0 (m, 8, aryl), 5.32 (s, 2, CH at C-1,1′), 6.6–7.7 (m, 8, CH_2CH_2 at C-3,3′4,4′), 8.27 (s, 2, NH).

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60; mol wt, 264.36. Found: C, 81.78; H, 7.68; N, 10.53; mol wt 262 (osmometry).

The dinitrate salt was prepared in hot 10% aqueous nitric acid and recrystallized from 10% nitric acid: mp 235–236° with decomposition.

(16) The reported nmr spectra of 1-substituted 2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines indicate the presence of two conformers due to restricted acetyl group rotation: D. R. Dalton, K. C. Ramey, H. J. Gisler, Jr., L. J. Lendvay, and A. Abraham, *J. Amer. Chem. Soc.*, **91**, 6367 (1969).

Anal. Calcd for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.25; H, 5.79; N, 14.19.

meso-1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline (5b). **Method A. From Bishydrobromide Salt 4b.**—The procedure employed in the preparation of *dl*-diamine **5a** from hydrobromide salt **4a** was used with *meso*-bishydrobromide salt **4b** to yield *meso*-diamine **5b**, 100% yield, mp 82–86°. Recrystallization from heptane gave white prisms: mp 86–88°; λ_{max} (EtOH) 267 nm (ϵ 920), 275 (895); nmr ($CDCl_3$) τ 2.7–3.3 (m, 8, aryl), 5.40 (s, 2, CH at C-1,1′), 6.5–7.5 (m, 8, CH_2CH_2 at C-3,3′,4,4′), 8.08 (s, 2, NH).

Method B. Hydrogenation of 1,1′-Biisoquinoline Hydrochloride.—A solution of 1.00 g of 1,1′-biisoquinoline in 100 ml of 95% ethanol containing 2 ml of concentrated hydrochloric acid was shaken with hydrogen in a Parr apparatus (50 psi, 25°) until 4 mol equiv of hydrogen was absorbed (5.5 hr). The catalyst was filtered and the filtrate concentrated to near dryness. The residue was treated with 20 ml each of 10% aqueous sodium hydroxide solution, ethanol and tetrahydrofuran; the resulting clear solution was concentrated to dryness and the residue extracted four times with ether. The dried ether extracts were combined and concentrated to yield 0.94 g of a viscous, pale yellow oil; crystallization from heptane gave 0.34 g of crystals, mp 60–85°; recrystallization from heptane gave diamine **5b** as prisms, mp 85–88°.

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60; mol wt, 264.36. Found: C, 81.96; H, 7.63; N, 10.44; mol wt, 268 (osmometry).

The **dinitrate** salt was prepared in hot 10% aqueous nitric acid and recrystallized from water, mp 228–229°, with decomposition and previous softening.

Anal. Calcd for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.77; H, 5.70; N, 14.19.

Diamines **5a** and **5b** react with group VIII metal chlorides to produce colors in aqueous ethanol as follows: nickel(II), greenish; cobalt(II), pink; iridium(IV), yellow-orange; iron(III), yellow; iron(II) with **5a**, yellow-orange. Ferrous chloride with **5b** gave a slight greenish color which after *ca.* 24 hr became deep blue; longer standing intensified the blue color which is produced within 1–2 hr by bubbling air through the solution, or by heating on the steam bath. With **5a** no blue color is produced under these conditions; **5a** could not be made to react with ferrous salts to produce a blue color under any conditions tested.

Samples of pure, white, crystalline *meso*-diamine **5b** on standing at room temperature became yellow after a few days. After several weeks the samples became oily with an odor of isoquinoline. For example, a sample stored *ca.* 1 month had its melting point lowered to 82–86° and its ultraviolet spectrum had changed—λ_{max} (EtOH), 259 nm (ϵ 1350), 267 (1470), 275 (1320), 290–310 sh (320), 323 (240). In contrast to pure **5b** it immediately gave a deep inky blue color with ferrous chloride; λ_{max} (aqueous EtOH) 550, 635 (most intense), 656, 658 nm. 3,3′,4,4′-Tetrahydro-1,1′-biisoquinoline (**10**) was found to give the same blue color and absorption maxima with ferrous chloride. Diamine **10**[9] has λ_{max} (EtOH) 258 nm (ϵ 15,400), but no strong bands near 323 nm. 1,1′-Biisoquinoline has λ_{max} (EtOH) 274 nm (ϵ 8500), 286 (7900), 312 (7400), 324 (10,700); it produces a pink color with aqueous ethanolic ferrous chloride. Isoquinoline has λ_{max} (EtOH) 260 nm (ϵ 3700), 267 (3700), 271 (3700), 308 (2500), 320 (2700)[17]; it produces a yellow color with ferrous chloride.

dl-8-Methyl-5,6,7,9,10,11,15b,15c-octahydrodiisoquino[2,1-*c*:1′,2′-*e*]imidazolinium Bromide (7a). **Procedure A. Hydrolysis of 3a.**—*dl*-2,2′-Diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline, **3a** (0.50 g), in 10 ml of concentrated hydrobromic acid was heated under reflux for 26 hr. The solution was concentrated to dryness and the residue diluted with water to precipitate 0.13 g (26%) of recovered **2a**, mp 212–218°. The filtrate was concentrated to dryness and the residue triturated with 2-propanol to yield 0.26 g (49%) of crude imidazolinium salt **7a**, mp 270–280°; recrystallization by dissolving in ethanol and precipitating with ether gave small, flat, square prisms, 0.17 g, mp 280–285°.

The above procedure applied to *meso* epimer **3b** (0.5 g) (49-hr reflux) gave 0.10 g (20%) of recovered **3b**, mp 230°, and 0.28 g (47%) of bishydrobromide salt **4b**, mp 265–268°, as the only crystalline product. Shorter reaction periods gave larger amounts of recovered reactant **3b** and less **4b**.

Procedure B.—A solution of *dl*-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (**5a**, 1.0 g) and ethyl acetimidate hydrochloride (0.54 g) in 10 ml of absolute ethanol was heated under reflux for 9 hr.[5,18] The solution was cooled and the filtrate diluted with 300 ml of ether and let stand overnight. White crystals separated, 1.0 g, mp 230–260°, believed to be *dl*-8-methyl-5,6,7,9,10,11,15b,15c-octahydrodiisoquino[2,1-c:1′,2′-*e*]imidazolinium chloride complexed with acetic acid:[19] ν (KBr) 1680 cm^{-1} (C=O, acetate), 1605 (C=N$^+$); nmr (D_2O) 7.47 (s, $CH_3C{=}N^+$), 7.58 (s, CH_3CO_2H). In a parallel 2.0-g run employing a 22-hr reflux period there was obtained 2.3 g of this crude chloride salt, mp 230–275°. Attempts to obtain the pure chloride salt free of acetic acid by crystallization from various solvents were unsuccessful. The crude material (1.0 g) was dissolved in 20 ml of concentrated hydrobromic acid and concentrated to dryness in vacuum. Crystallization of the residue from water gave 0.88 g (63%) of hydrated bromide salt **7a**, mp 280–283°, with prior melting at 110–115° and loss of solvent. The hydrated material was dissolved in ethanol and precipitated with ether to give small prisms of anhydrous **7a**: mp 275–280°, with previous softening; ν (KBr) 1610 cm^{-1} (C=N$^+$), 1570 (C=C); nmr (D_2O) τ 2.45 (m, 8, aryl), 4.55 (s, 2, CH at 15b, 15c), 6.02 (m, 4, CH_2 at C-3,3′), 6.80 (m, 4, CH_2 at C-4,4′), 7.47 (s, 3, CH_3), sodium 3-trimethylsilylpropanesulfonate internal standard.

Anal. Calcd for $C_{18}H_{21}BrN_2$: C, 65.05; H, 5.73; Br, 21.64; N, 7.59. Found: C, 64.90; H, 5.71; Br, 21.74; N, 7.48.

A 0.10-g sample of imidazolinium bromide salt **7a** in a solution of 5 ml each of concentrated hydrobromic acid, acetic acid, and water was heated under reflux for 48 hr. Concentration to near dryness and dilution of the residue with 1 *N* hydrobromic acid gave, in successive crops, 0.09 g of recovered **7a** hydrate, mp 280–283° after prior melting at 110° and resolidifying; infrared spectrum was identical with that of **7a** hydrate.

dl-2-Acetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (6a).—A solution of *dl*-8-methyl-5,6,7,9,10,11,15b,15c-octahydrodiisoquino[2,1-c:1′,2′-*e*]imidazolinium bromide (**7a**, 0.20 g) in a solution of 5 ml each of ethanol and 10% aqueous sodium hydroxide was heated under reflux for 18.5 hr. The solution was concentrated to a volume of 3 ml and chilled at 0° to precipitate 0.13 g of crystals, mp 121–135°. Recrystallization from benzene gave small flat prisms, mp 143–144°, with a change near 135° to chunky prisms. The imidazolinium chloride salt described above may also be employed in this preparation (99% yield of **6a**).

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.34; H, 7.14; N, 8.99.

A solution of 7.1 mg of monoamide **6a** in 1 ml of acetic anhydride containing 1 drop of sulfuric acid was warmed on the steam bath for 40 min. Water (15 ml) was added and the mixture chilled to 0° and subsequently filtered to yield 5.6 mg of *dl*-bisamide **3a**, mp 212–213° (mixture melting point with authentic **3a** undepressed).

A solution of 0.20 g of **6a** in 4.0 ml of concentrated hydrobromic acid was heated under reflux for 26.5 hr. Concentration to dryness gave crystals which were triturated with 25 ml of ether and filtered to yield 0.22 g of imidazolinium salt **7a**, mp 250–270°; recrystallization from ethanol–ether gave a sample, mp 275–285°; infrared spectrum identical with that of an authentic sample of **7a**.

A solution of 0.20 g of **6a** in 1.3 ml each of concentrated hydrobromic acid, water, and acetic acid was heated under reflux for 48 hr. Concentration to near dryness, followed by dilution with 5 ml of water and chilling to 0°, gave 0.17 g of bishydrobromide salt **4a**, mp 294–298° (mixture melting point with authentic sample undepressed).

dl-5,6,7,9,10,11,15b,15c-Octahydro-8H-diisoquino[2,1-c:1′,2′-*e*]imidazole (8a).—A solution of diamine **5a** (0.52 g, 0.002 mol) and 0.15 ml of 37% formalin in 5 ml of dioxane was heated on the steam bath for 2.7 hr and kept at 25° for 15 hr. Concentration of the solution to dryness gave 0.55 g (100%) of crude **8a**, mp 110–125°. Recrystallization from dilute ethanol gave 0.39 g (72%) of **8a**, colorless prisms, mp 125–128°.

(17) J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.*, 3318 (1951).

(18) S. M. McElvain and J. W. Nelson, *J. Amer. Chem. Soc.*, **64**, 1825 (1942).

(19) Many substituted 2-imidazolines form stable complexes with acetic acid: J. L. Riebsomer, *J. Amer. Chem. Soc.*, **70**, 1629 (1948).

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14; mol wt, 276.37. Found: C, 82.71; H, 7.20; N, 10.03; mol wt, 280 (osmometry).

meso-**5,6,7,9,10,11,15b,15c-Octahydro-8H-diisoquino[2,1-*c*:1′,2′-*e*]imidazole (8b).**—The procedure employed with diamine **5a** was used with 0.52 g of diamine **5b** to yield an oil which was extracted with hot heptane. Chilling the extracts gave 0.30 g (55%) of **8b**, mp 90–93; concentration of the filtrate gave an additional 0.04 g, mp 80–90° (62% total). Recrystallization of the first crop from heptane gave prisms, mp 90–92°.

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14; mol wt, 276.37. Found: C, 82.86; H, 7.37; N, 10.02; mol wt, 280 (osmometry).

1,1′-Biisoquinoline (12).—*dl*-1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline, **5a** (1.0 g), in 25 ml of *p*-cymene was heated under reflux with 0.3 g of 10% palladium–charcoal for 27 hr; a stream of nitrogen was passed over the surface of the liquid during the heating. The catalyst was filtered and extracted several times with hot *p*-cymene. The filtrate and extracts were combined and concentrated to dryness under reduced pressure and the crystalline residue triturated with heptane; after the mixture chilled at −15° for several hours the mixture was filtered to yield 0.70 g (72%) of crystalline 1,1′-biisoquinoline, mp 155–163°. Recrystallization from benzene–heptane gave large, chunky prisms, 0.56 g, mp 167–168°, lit.[20] mp 162–163°; on admixture with an authentic sample the melting point was not depressed (infrared spectrum identical). Parallel runs gave 65–70% yields of 1,1′-biisoquinoline. Best yields were obtained with 10% palladium–charcoal catalyst of high activity and recrystallized, high purity diamine.

meso-**1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline (5b)** was employed in the above procedure to provide 1,1′-biisoquinoline in 66% yield, mp 158–166° before recrystallization.

5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-biisoquinoline (13).—1,1′-Biisoquinoline (2.56 g, 0.01 mol) dissolved in 100 ml of acetic acid was shaken with 1.0 g of 5% rhodium–charcoal catalyst and hydrogen (50 psi, 25°) in a Parr apparatus for 80 hr; approximately 2 mol equiv of hydrogen was absorbed. The catalyst was filtered and washed with acetic acid, and the filtrate concentrated to near dryness *in vacuo*. The residue was treated with 20 ml of 10% aqueous sodium hydroxide, 10 ml of ethanol, and 10 ml of tetrahydrofuran. The clear solution was concentrated to dryness and the residue extracted with methylene chloride; the dried extracts were concentrated to yield 2.45 g of dark oil. Extraction of the oil with hot heptane and treatment with Darco-G 60 decolorizing carbon, followed by concentration and chilling at −15°, gave 1.35 g of white crystals, mp 93–120°, a mixture of **13** (*ca.* $^2/_3$; 34% yield) and 1,1′-biisoquinoline (*ca.* $^1/_3$) which could not be separated completely by fractional crystallization from heptane. The mixture was separated by preparative scale tlc on silica gel (Mallinckrodt Silicar 7GF) with ether developer; the fast-moving component was pure 1,1′-biisoquinoline, mp 162–163°, identified by mixture melting point and infrared spectrum. The slower moving component was **13** containing some 1,1′-biisoquinoline which was very difficult to remove completely. Column chromatography on basic alumina (elution with heptane) gave a sample (fast-moving component) which was recrystallized from heptane, mp 135–139°.

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60; mol wt, 264.36. Found: C, 81.74; H, 7.34; N, 10.61; mol wt, 264 (mass spectrometry).

A 0.29-g sample of **13**, 0.15 g of 10% palladium–charcoal and 50 ml of *p*-cymene were heated under reflux in a nitrogen atmosphere for 29 hr. Filtration of the catalyst, followed by concentration of the filtrate to dryness, gave an oil which was triturated with heptane to yield 0.24 g of crystals, mp 143–154°; recrystallization from benzene–heptane gave chunky prisms of 1,1′-biisoquinoline, mp 156–163°, identified by mixture melting point and infrared spectrum.

dl-**2,2′-Diacetyl-1,1′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (18a).**[21]—A mixture of 1.2 g of *dl*-diamide **2a** and 25 ml of acetic acid was treated with 1.3 g of N-bromosuccinimide. Complete solution of the reactants was rapidly obtained, accompanied by a small temperature rise. After 24 hr at room temperature, the solution was diluted with 50 ml of water; the white precipitate was filtered and washed well with water; 1.7 g (97%), mp 192–195°, was obtained. Recrystallization from benzene gave felted needles, mp 212–214°.

Anal. Calcd for $C_{22}H_{18}Br_2N_2O_2$: Br, 31.83; N, 5.58; mol wt, 502. Found: Br, 31.95; N, 5.56; mol wt, 526 (osmometry).

meso-**2,2′-Diacetyl-1,1′-dibromo-1,1′2,2′-tetrahydro-1,1′-biisoquinoline (18b).**[21]—The procedure employed in the preparation of **18a** gave with *meso*-diamide **2b** an 84% yield of **18b**, fine white powder, mp 231–232° after recrystallization from benzene.

Anal. Calcd for $C_{22}H_{18}Br_2N_2O_2$: Br, 31.83; N, 5.58. Found: Br, 32 08; N, 5.50.

Hydrolysis of 18a and 18b.[21]—*dl*-Dibromo compound **18a** (0.7 g) was heated under reflux with a solution of 0.3 g of sodium hydroxide in 20 ml of 50% aqueous ethanol. The cooled solution was diluted with 12 ml of water and extracted with three small portions of ether; evaporation of the extracts gave 0.43 g of oil containing two components which were easily separated by glc (10 ft × $^1/_4$ in. column of 20% SE-52 on Chromosorb W; 190°). Isoquinoline (*ca.* 55% yield) came off the column first: retention time the same as isoquinoline; *m/e* (parent) 129; calcd for C_9H_7N, 129.15. The second component (*ca.* 40% yield) showed parent *m/e* values of 207 and 209 of nearly equal intensity; calcd for C_9H_6BrN, 208.06; mp 41–41.5°, lit.[22] mp 41.5–42.3° for 1-bromoisoquinoline.

Hydrolysis of the *meso* isomer **18b**, under conditions comparable with those employed with **18a**, occurred more slowly; a reaction time of 11 hr was required to effect complete solution. The yield of liquid product from 1.4 g of **18b** was 0.89 g (*ca.* 95% total yield of approximately equal amounts of isoquinoline and 1-bromoisoquinoline, based on glc analysis).

Registry No.—**2a**, 25080-52-8; **2b**, 25055-08-7; **3a**, 25055-09-8; **3b**, 25062-09-3; **4a**, 25062-12-8; **4b**, 25062-13-9; **5a**, 25062-14-0; dinitrate salt of **5a**, 25062-15-1; **5b**, 25062-16-2; dinitrate salt of **5b**, 25062-17-3; **6a**, 25062-18-4; **7a**, 25062-19-5; **8a**, 25080-54-0; **8b**, 25080-55-1; **13**, 25056-48-8; **18a**, 25062-20-8; **18b**, 25062-21-9.

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3,4-Dihalopyrroles[1a,b]

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Eleven new 3,4-dichloro- and 3,4-dibromopyrroles were synthesized and studied. The chlorine atoms in the 3,4 positions were found to be unreactive to potassium fluoride in DMF, to hydrazine, and to lithium aluminum hydride. Further evidence is presented that halogenation with sulfuryl chloride proceeds by a free-radical mechanism. These compounds, together with those which had been prepared previously, form the basis of a representative spectral study of the 3,4-dihalopyrroles. Empirical band assignments were made for infrared spectra measured in both Nujol mulls and in carbon tetrachloride. The effect of halogen substitution on the ultraviolet spectra of pyrroles in ethanol was determined. The type of halogen present had no appreciable effect on the proton magnetic resonance (pmr) spectra of these compounds.

One of the objectives of the research program conducted in these laboratories is the study of the effects of electronegative substituents on the properties of porphyrins, dipyrromethenes, and their metal chelates. The halogens have been chosen as substituents to avoid the complications arising from the conjugative interactions of the pyrrole ring with unsaturated groups. The building blocks of these porphyrins and dipyrromethenes are the appropriately substituted 3,4-dihalopyrroles whose chemistry is described in this work.

Fischer synthesized several 3,4-dichloropyrroles,[2] including the parent 3,4-dichloropyrrole.[3] There are also some scattered reports[4,5] of other 3,4-dihalopyrroles in the literature. However, at present there are not enough data to draw conclusions concerning the attenuation of pyrrole reactivity caused by a 3,4-dihalo grouping, since previous studies[4,6-9] of reactivity were made exclusively with α- or β-monohalopyrroles.

Spectral studies of halopyrroles and in particular of 3,4-dihalopyrroles have not been reported previously. in an infrared study[10] only one halopyrrole was included. Work cited in the references of a recent review[8] and later ultraviolet studies[11-13] exclude all halopyrroles. In a study[5] of the halogenation of methyl pyrrole-2-carboxylate the ultraviolet and pmr spectra are reported for several halopyrroles including methyl 3,4-dichloropyrrole-2-carboxylate and methyl 3,4,5-trichloropyrrole-2-carboxylate. Although several other 3,4-dihalogen-substituted pyrroles are known,[2-4] spectral data are not available for these compounds.

Therefore, it is the purpose of this work to make available new intermediates for the synthesis of haloporphyrins and dipyrromethene chelates, to determine some basic rules of reactivity in this series, to measure the ultraviolet, infrared, and proton magnetic resonance spectra, and to set up spectra–structure correlations for this series of dihalopyrroles. Ultimately, it is hoped to obtain firm conclusions concerning the effects of electronegative substitution in porphyrins and dipyrromethene chelates.

Results

A terse summary of the reaction paths followed in the interconversion and preparation of the compounds utilized in this comprehensive study of 3,4-dihalopyrroles is displayed in Scheme I. Reference to the formulas in this scheme will be made in the following: Results, Discussion, and Experimental Section.

Infrared Spectra.—Table I contains a summary of the N—H, C=O, and C=C stretching frequencies of 3,4-dihalopyrroles. The solution spectra were useful in observing the unassociated N—H stretching vibration and the various C—H saturated modes. Since solid state and solution spectra were significantly the same, unless otherwise indicated, the Nujol mull spectra will be discussed.

The N—H stretching region in solution spectra contains a sharp peak in the range of 3448–3497 cm^{-1} characteristic of an unbonded or "free" N—H vibration. A broader absorption is also present in the range of 3215–3311 cm^{-1} for all compounds possessing either a carbonyl or a hydroxyl group, indicating some intermolecular association of the >C=O···H—N< or the >O···H—N< type. The mull spectra show the "associated" peak in the region of 3155–3378 cm^{-1} for most halopyrroles and sharp peaks at 3436 and 3460 cm^{-1} for **7** and **13**, respectively. The values at the extremes of this range occur with compounds whose structure possesses a hydroxy group depending on whether the halo substituents are chloro (**18**, **19**) or bromo (**27**). The esters absorb in a narrow region at about 3270, the aldehydes somewhat more variably at about 3230, and the dipyrrylmethanes at about 3220 cm^{-1}. The observed N—H stretching frequency of 3,4-dichloro-5-methylpyrrole-2-carboxylic acid (**10**) measured in Nujol is high at 3448 cm^{-1}, indicating that through carboxylate dimer formation the NH group becomes inaccessible to hydrogen bonding in the solid phase. As larger halogens are substituted in the series **2**, **25**, **30**, there is a gradual drop in the N—H absorption frequency contrary to the expectation based on electronegativity. This effect could be explained in terms of the considerable distortions in the pyrrole

(1) (a) Abstracted in part from a thesis submitted by R. J. Motekaitis to the faculty of Illinois Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) This work was supported by a research grant, GM11621, from the National Institute of General Medical Sciences, U. S. Public Health Service. (c) To whom inquiries may be addressed: Texas A & M University.

(2) H. Fischer and E. Elhardt, *Z. Physiol. Chem.*, **257**, 61 (1939).

(3) H. Fischer and K. Gangl, *ibid.*, **267**, 188 (1941).

(4) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. 1, Academische Verlags GmbH, Leipzig, 1934.

(5) P. Hodge and R. Rickards, *J. Chem. Soc.*, 459 (1965).

(6) A. H. Corwin and G. G. Kleinspehn, *J. Amer. Chem. Soc.*, **75**, 2089 (1953).

(7) A. Treibs and H. Kolm, *Justus Liebigs Ann. Chem.*, **614**, 176 (1958).

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(9) K. W. Doak and A. H. Corwin, *J. Amer. Chem. Soc.*, **71**, 159 (1949).

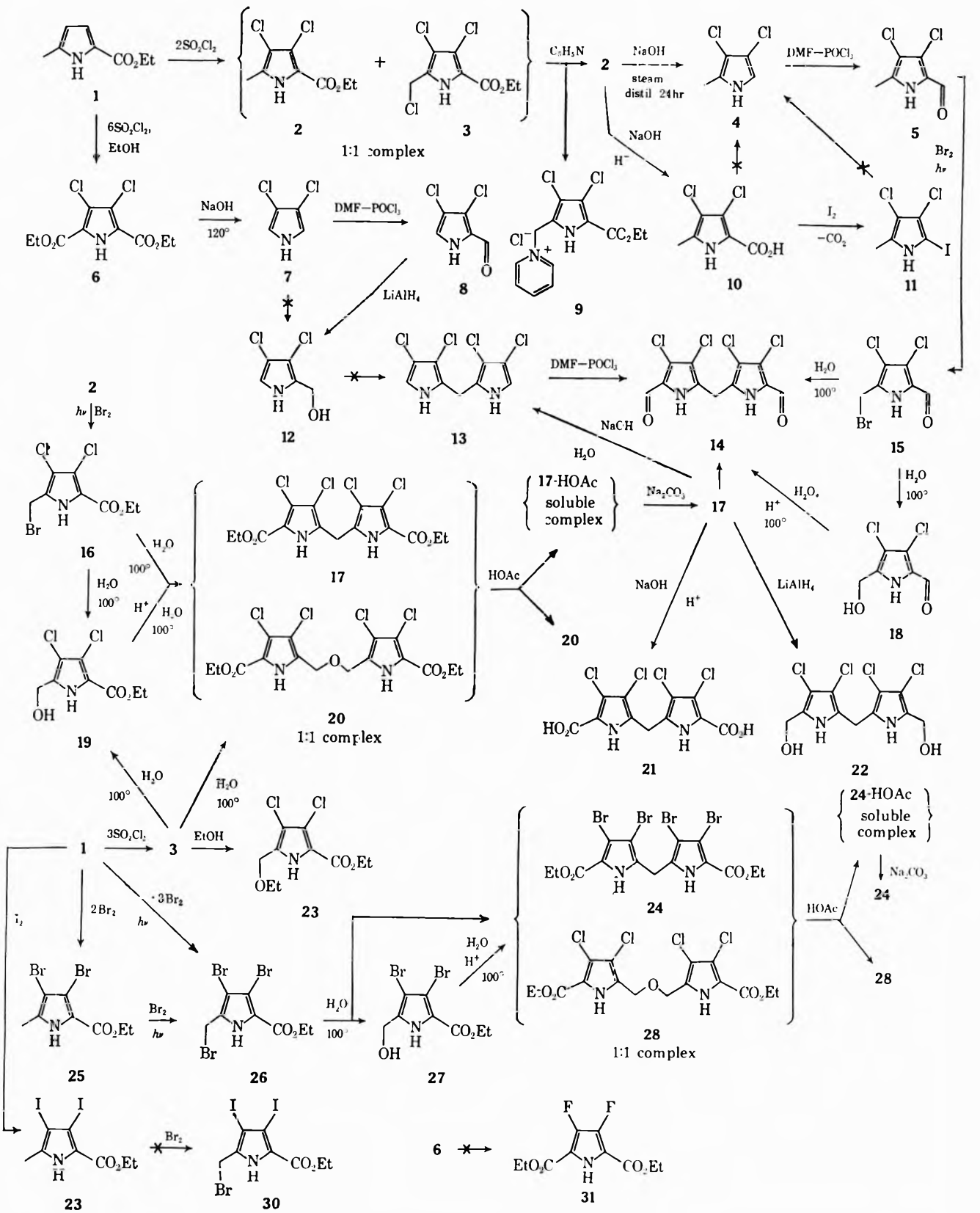
(10) U. Eisner, *J. Chem. Soc.*, 971 (1958).

(11) F. Erb-Debryne, *Ann. Chim.* (Paris), **9**, 73 (1964).

(12) R. Hinman and S. Theodoropulos, *J. Org. Chem.*, **28**, 3052 (1963),

(13) P. Chiorboli, A. Rastelli, and F. Nomichioli, *Theor. Chem. Acta.* **5**, 1 (1966).

Scheme I



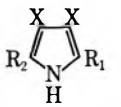
ring geometry caused by mutual repulsion between the halo groups in the 3,4 positions.

The ester carbonyl absorption frequency of 3,4-dihalopyrroles measured in Nujol is rather constant at 1667–1669 cm^{-1} unless either a hydroxy group (**19**, **27**) or another unsaturated substituent (**6**) is present. For compounds also measured in solution, this absorption is on the average about 3–5 cm^{-1} higher. The aldehyde carbonyl stretching frequencies are about 33–42 cm^{-1} lower than those of the analogous esters.

3,4-Dihalopyrroles possess two bands in the C=C stretch region of 1600–1470 cm^{-1}. The first band is weak and is ascribed to the asymmetrical stretch. The second band is somewhat stronger and is ascribed

TABLE I

INFRARED MAXIMA OF N—H, C=O, AND C=C STRETCHING MODES IN 3,4-DIHALOPYRROLES



Compd no.	X	R_1	R_2	Medium	cm⁻¹ N—H		C=O		C=C	
1	H	CO_2Et	Me	N[a]		3367	1681		1577	1497
				C[b]	3472	3311	1672		...[c]	1490
2	Cl	CO_2Et	Me	N		3300	1669		1563	1493
				C	3472	3311	1672			1490
3	Cl	CO_2Et	CH_2Cl	N		3279	1669		1560	1488
				C	3442	3268	1698	1673		1488
16	Cl	CO_2Et	CH_2Br	N		3279	1667		1558	1488
				C	3442	3268	1698	1672		1488
17	Cl	CO_2Et	PM[d]	N		3215	1669		1563	1484
				C		3215	1664			1488
19	Cl	CO_2Et	CH_2OH	N		3175	1681		1555	1493
23	Cl	CO_2Et	CH_2OEt	N		3279	1678		1563	1493
				C	3448	3268	1672			1486
20	Cl	CO_2Et	PMOM[e]	N		3268	1669		1560	1488
6	Cl	CO_2Et	CO_2Et	N		3279	1709		1531	
				C	3448	3268	1672			1486
9	Cl	CO_2Et	$CH_2Py^+Cl^-$	N		...[f]	1684		1555	1481
	Cl	CO_2Et	$CH_2Py^+Br^-$	N		...[f]	1686		1555	1481
8	Cl	CHO	H	N		3215	1642			1481
				C	3448	3247	1656			1481
5	Cl	CHO	Me	N		3215	1634		1558	1488
				C	3448	3236	1637			1493
15	Cl	CHO	CH_2Br	N		3185	1650		1553	1484
				C	3436	3236	1639			1488
14	Cl	CHO	PM	N		3226	1642		1553	1486
18	Cl	CHO	CH_2OH	N		3155	1639			1471
7	Cl	H	H	N	3436				1538	1513
				C	3497				1534	1493
13	Cl	H	PM	N	3460				1563	1493
				C	3472				1563	
10	Cl	CO_2H	Me	N	3448		1664		1570	1504
25	Br	CO_2Et	Me	N		3279	1669		1558	1488
				C	3448	3279	1667			1486
26	Br	CO_2Et	CH_2Br	N		3268	1667		1558	1488
24	Br	CO_2Et	PM	N		3205	1669		1563	1485
27	Br	CO_2Et	CH_2OH	N		3378	1658		1553	1484
29	I	CO_2Et	Me	N		3289	1669		1543	1475
				C	3448	3268	1667			1479

[a] Nujol mull. [b] Carbon tetrachloride solution. [c] Peaks in the 1550-cm^{-1} region are obscured in the 0.2-mm cell by absorption due to solvent. [d] Pyrrylmethyl group with identical substituents on the pyrrole ring. [e] Pyrrylmethoxymethyl group with identical substitutents on pyrrole ring. [f] Very broad absorption.

to the symmetrical mode.[14] In the ester series, the first band is fixed at 1558 ± 5 cm^{-1} except for the diester **6** and for 3,4-dichloropyrrole **7** where it is low at 1531 and 1538 cm^{-1}. The values for the aldehydes are similar to those of the esters. The second band is more variable with most values falling around 1488 cm^{-1}, which is about 12 cm^{-1} lower than the corresponding band in the unhalogenated[10] pyrrole compounds.

All the ethyl esters show a band at 1285 cm^{-1} and one at about 1115 cm^{-1}, indicative of the C—O stretch which is absent in the aldehyde spectra. Another group of bands present are at about 1440, 1365, 1150, 1050, 875, and 775 cm^{-1}, all of which are assigned to the presence of the ethyl group. The bands at 1390 cm^{-1} are due to a methylene group adjacent to a double bond and the bands at 1220 cm^{-1} are the C—O stretching vibrations on the ethyl side of the oxygen. All of the above bands are within about 5 cm^{-1} except for the hydroxymethyl compounds. Three aldehydes (**5**, **15**, **18**) show the CH deformation vibration at 840 and dipyrrylmethane **14** at 853 while that of 3,4-dichloropyrrole-2-aldehyde occurs at 785 cm^{-1}. All aldehydes studied show bands at 1360 and 1260 cm^{-1} and in the region of 1230–1160 cm^{-1}.[15] The four tetrasubstituted pyrrolealdehydes (**5**, **15**, **18**, **14**) possess a band at 1410 cm^{-1} which can be ascribed to a methylene vibration. All aldehydes show a band at 1059, but only the tetrasubstituted aldehydes show, in addition, an absorption at 1107 cm^{-1}. This band is ascribed to a C—C stretch involving the exocyclic carbon of the substituent while the former is probably due to a C—C stretch involving the formyl groups.

The two characteristic aldehyde CH stretch and combination[15] modes appear in the expected range

(14) Assignments are made by analogy to the study described in ref 10.

(15) L. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1962.

Table II

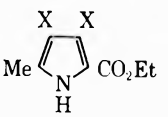
Ultraviolet Spectra of Substituted 3,4-Dihalopyrroles

Compd no.	Substituents 2	3	4	5	Medium	Band I λ, mμ	Band I ε	Band II λ, mμ	Band II ε
...[a]	H	H	H	H	E[b]	183		211	15,000
7	H	Cl	Cl	H	E	208	5,240		
1	CO_2Et	H	H	Me	E	231	3,320	277	18,690
2	CO_2Et	Cl	Cl	Me	E	245	6,950[c]	275	15,440
25	CO_2Et	Br	Br	Me	E	255	8,440[c]	278	15,350
29	CO_2Et	I	I	Me	E	265	11,700[c]	277	15,560
...[a]	CHO	H	H	H	E	252	5,000	290	16,600
8	CHO	Cl	Cl	H	E	265	7,860[c]	290	13,440
5	CHO	Cl	Cl	Me	E	270	6,310[c]	304	17,080
13	H	Cl	Cl	PM[d]	C[e]	250	5,700[f]		
17	CO_2Et	Cl	Cl	PM	C	247	14,700[c]	270	23,800
14	CHO	Cl	Cl	PM	C	270	5,300	294	8,300
								309	7,900

[a] Reference 16. [b] Absolute ethanol. [c] The extinction coefficient reflects only the intensity measured with no correction made for overlapping peaks. [d] PM, pyrrylmethyl group with identical substituents on the pyrrole ring. [e] Spectro-Grade chloroform. [f] Very sharp peak.

but higher than average. The first band is somewhat variable between 2874 and 2857, while the second is stationary at 2833 cm^{-1}. The pyrrole CH nuclear vibrations are constant at 3160 cm^{-1} irrespective of the other α substituent.

Ultraviolet Spectra.—The ultraviolet spectra of representative 3,4-dihalopyrroles measured in solution are summarized in Table II. Since there is no general agreement on the theoretical interpretation of the spectrum of pyrrole,[16] only the observed effects of substituents can be presented for 3,4-dihalopyrroles. The substitution of two chlorine atoms into the β positions of pyrrole produces a new band at 208 mμ (ε 5240). For the corresponding dimethyl compound this band occurs at 205 mμ (ε 4400).[17] Similar substitution of chlorine atoms into β positions of pyrrole-2-aldehyde shifts band I toward band II but has no effect on the position of band II and lowers its intensity by 20%. In the series X = H, Cl, Br, and I for structure **32**, band I, a shoulder, increases by about 10 mμ



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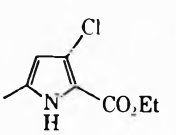
for each successive derivative with its intensity also increasing in steps of 3000 units. Band II remains stationary at about 277 mμ (ε 15,500) after an initial drop of 20% in intensity upon halogenation. The introduction of a methyl group into 3,4-dichloropyrrole-2-aldehyde **8** causes a small bathochromic shift in band I and a large one in band II going from 290 mμ (ε 13,400) to 304 (17,100). Substitution of a formyl group for a carbethoxy group shifts both band I and band II to longer wavelength.

An exceptionally large difference in absorption becomes apparent in comparing the dipyrrylmethane **13** with the pyrrole **7**. A part of this shift may be explained by changing of solvents and another part by the introduction of a methylene group, but the bulk of the shift represents evidence for possible electronic interaction between the two π systems within the dipyrrylmethane molecule. A similar conclusion could be reached on comparing the pairs of spectra of **17** and **2** and of **14** and **5**, although in these cases the spectrum of each dipyrrylmethane is not so dramatically different from the spectrum of its corresponding monopyrrole.

Proton Magnetic Resonance.—The proton magnetic resonance spectra of 3,4-dihalopyrroles and the corresponding dipyrrylmethanes are summarized in Tables III and IV. The resonance signal of the ethyl group in carbethoxy compounds is generally unaffected by substituents to about 0.1 ppm and occurs as a triplet and a quartet at τ 8.65 and 5.75, respectively. The ring methyl gives rise to a sharp singlet at 7.72 ± 0.06 and the methylene gives a sharp singlet at τ 5.48 ± 0.10. The methylene joining two pyrryl groups in dipyrrylmethanes occurs as a sharp singlet at τ 6.0 in deuteriochloroform and 0.25 ppm lower in pyridine. This value drops to τ 3.5 upon substitution of bromine (see Table IV). In general, the proton resonance signal for NH could not be detected. The pmr spectra of 3,4-dihalogenated pyrroles are thus found to be relatively simple and therefore provide a valuable diagnostic check for the characterization of new as well as of old pyrrole compounds.

Discussion

The 1:1 compound adducts isolated in this work are the following pairs: **2** and **3**, **33** and **34**, **17** and **20**, and **24** and **28**. Each pair possesses a sharp melting point and with the exception of **33** and **34** can be separated chemically into its individual components.



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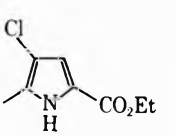


34

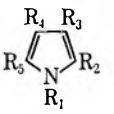
Elemental analyses and pmr spectra are also in accord with the 1:1 compound structures. Two modes of binding can be considered: charge transfer and hydrogen bonding. It is probable that the pyrrole ring can function as a π acid when it possesses electronega-

(15) H. Jaffee and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York, N. Y., 1962, p 351.

(17) R. Hinman and S. Theodoropulos, *J. Org. Chem.*, **28**, 3052 (1963).

TABLE III

PROTON MAGNETIC RESONANCE SPECTRA[a] OF 3,4-DIHALOPYRROLES

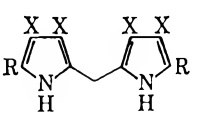


Substituents, [chemical shifts[b] (multiplicity)]					Compd
R_1	R_2	R_3	R_4	R_5	no.
H	CO_2Et [8.73 (3),[c] 5.82 (4)]	H [4.25 (3) (J = 3.9[d])]	H [3.38 (3) J = 3.9)]	Me [7.77]	1
H	CO_2Et [8.65 (3), 5.75 (4)]	Cl	Cl	Me [7.78]	2
H	CO_2Et [8.65 (3), 5.77 (4)]	Br	Br	Me [7.75]	25
H	CO_2Et [8.65 (3), 5.78 (4)]	I	I	Me [7.66]	29
H	CO_2Et [8.63 (3), 5.73 (4)]	Cl	Cl	CO_2Et [8.63 (3), 5.73 (4)]	6
H	CO_2Et [8.63 (3), 5.73 (4)]	Cl	Cl	CH_2Cl [5.55]	3
H	CO_2Et [8.62 (3), 5.67 (4)]	Cl	Cl	CH_2Br [5.58]	16
H	CO_2Et [8.67 (3), 5.77 (4)]	Cl	Cl	CH_2OH [5.43]	19
H	CO_2Et [8.56 (3), 5.63 (4)]	Br	Br	CH_2Br [5.53]	26
H	CO_2Et [8.61 (3), 5.73 (4)]	Br	Br	CH_2OH [5.38]	27
H	CHO [0.36 (2) (J = 1.1)]	Cl	Cl	H [2.91 (2) (J = 1.1)]	8
H	CHO [0.86]	Cl	Cl	Me [7.69]	5
H	H [3.38 (2) (J = 3.1)]	Cl	Cl	H [3.38 (2) (J = 3.1)]	7
H [6.07]	Cl	Cl	Cl	Cl	
H	CO_2Et [8.70 (3), 8.65 (3), 5.85 (4), 5.68 (4)]	H (Cl) [3.50]	Cl (H) [3.45]	Me [7.78[e]]	33, 34

[a] Measured in deuteriochloroform at ~37°. [b] Relative to internal TMS, given in τ units. [c] Multiplicity of band if split. [d] J is given in hertz. [e] Could not be resolved.

TABLE IV

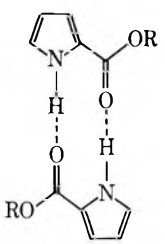
PROTON MAGNETIC RESONANCE SPECTRA OF DIPYRRYLMETHANES



Solvent	Bridge [chemical shifts[a]]	Substituents [chemical shifts[a] (multiplicity)] R	X	Other		Compd no.
$CDCl_3$	CH_2 [5.93]	CO_2Et [8.61 (3),[b] 5.78 (4)]	Cl	NH [−0.88]		17
$CDCl_3$	CH_2 [6.04]	CO_2Et [8.63 (3), 5.92 (4)]	Cl	CH_3CO_2H[c] [7.96]		
$CDCl_3$	CHBr [3.52]	CO_2Et [8.66 (3), 5.67 (4)]	Cl			
$CDCl_3$	CH_2 [6.09]	H [3.46 (2) (J = 2.9[d])]	Cl			13
$CDCl_3$	CH_2 [5.57]	CH_2OH [6.23, 6.8[f]]	Cl	Et_2O[e] [8.92 (3), 6.54 (4)]	NH [1.90 (2)]	22
Pyridine	CH_2 [5.75]	CO_2Et [8.98 (3), 5.85 (4)]	Br	$C_2H_4Cl_2$[c] [6.28]		24
DMSO	CH_2 [6.07]	$CONHNH_2$ [4.02]	Cl			
DMSO	CH_2 [6.05]	$CONHNHSO_2Ph$ [2.42 (2), 1.92 (3), 0.38, 0.08, −1.90]	Cl			
DMSO	CH_2 [5.93]	CHO [0.47]	Cl	NH [6.4[f]]		14

[a] Relative to internal TMS, given in τ units. [b] Multiplicity of split band. [c] Solvent cocrystallized. [d] J is given in hertz. [e] Residual ether from reaction solvent. [f] Very broad band.

tive chlorine or bromine and carbethoxy substituents. However, charge transfer complexes can form only between two dissimilar molecules, *i.e.*, between pairs of either strong donor and good to moderate acceptor molecules or strong acceptors and moderate to good donors.[18] *A priori*, it then becomes unlikely that pairs of such similar molecules as **2** and **3**, **33** and **34**, **17** and **20**, and **24** and **28**, or the case cited in the literature,[19] would form stable π complexes. Additional evidence was obtained to rule out charge-transfer interactions and to help support the more reasonable hydrogen-bonding mechanism **35**. The ultraviolet and



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the infrared spectra of **2**, **3**, and of equimolar solutions of **2** and **3** were measured, It was found that both electronic and vibrational spectra of the 1:1 solutions were composites of their corresponding individual spectra. These results help further to substantiate the lack of electronic interactions and therefore support the hydrogen bonding dimer **35**. This tendency to dimerize in dihalopyrrole esters and aldehydes is additionally evidenced by the considerably smaller "free" NH peak, the very large, broad "bonded" NH vibration, and the total absence of any free NH peak in the solution infrared spectrum of the dipyrrylmethane **17**. A molecular model of a strainless, totally hydrogen-bonded dimer of **17** was constructed as a verification of the interpretation of the above infrared results. Unfortunately, the solubility was too low for the determination of the molecular weight.

The isolation of the pair **33** and **34** offers an interesting observation. The fact that these intermediates were formed in equal amounts suggests that the sulfuryl chloride reaction in ether can proceed at least in part through a free-radical mechanism. Substitution into the 3 position, which has been deactivated by the adjacent carbethoxy group, can occur only by a homolytic attack,[5] whereas substitution into the 4 position can, in addition, occur also by electrophilic attack. Of course, further chlorination with sulfuryl chloride of the methyl side chain must occur by a free-radical mechanism.

Experimental Section

Materials and Apparatus.—The organic starting materials were Eastman Kodak practical grade and were used without further purification. The inorganic reagents were gererally of analytical grade. Solvents used were analytical grade except where large-scale recrystallizations were involved. The elemental analyses were determined by Alfred Bernhardt, Germany. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Solution infrared spectra were measured on a Beckman Model IR-8 spectrophotometer; Nujol mull spectra were obtained using a Perkin-Elmer Infracord. The proton magnetic resonance spectra were recorded on a Varian Associates Model A-60 spectrometer with readings relative to internal tetramethylsilane in τ units.[20] The ultraviolet specta were measured on an Applied Physics Corp. Cary Model 14 spectrophotometer.

Ethyl 5-Methylpyrrole-2-carboxylate (**1**).—The literature procedure[21,22] was found unsuitable for large-scale preparation. A solution of 332 g (4.8 mol) sodium nitrite in 500 ml of water was added dropwise to a cooled (below 20°) solution of 520 g (4.0 mol) of ethyl acetoacetate in 1560 g of glacial acetic acid. After 12 hr, the reaction mixture was divided into three equal parts, and each part in turn was treated with 176 g (1.33 mol) of 4,4-dimethoxy-2-butanone and 191 g (2.9 g-atoms) of zinc dust which was added portionwise to the well-stirred solution as rapidly as foaming permitted. The mixture was heated at 120° for 10 min and after slow cooling to 50° was poured into ice water and stirred for 1 hr. The orange solid was washed well with ice water, dried in air, and distilled *in vacuo* (short air condenser), bp 110–120° (0.1 mm), 130–160° (0.3 mm), until the pressure started rising. The distillate was recrystallized from Skellysolve B, yield 135 g (22%), mp 98–100° (lit.[22] mp 100°).

A by-product was isolated and recrystallized from hexane which is identical with the product obtained in 12.6% yield by omitting 4,4-dimethoxy-2-butanone from the above procedure: mp 83°; pmr ($CDCl_3$) τ 8.54 (t, 3), 5.50 (q, 2), 7.72 (s, 3); ir (Nujol) 1706 cm^{-1} (C=O).

Anal. Calcd for 2,5-dicarbethoxy-3,6-dimethylpyrazine, $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.36; H, 6.44; N, 11.26.

Ethyl 3,4-Dichloro-5-methylpyrrole-2-carboxylate (**2**).—An ice-cooled solution of 7.6 g (0.050 mol) of **1** in 100 ml of absolute ether was treated dropwise with 13.5 g (0.100 mol) of sulfuryl chloride over a 15-min period. The solvent was removed and the residue was dissolved in 50 ml of ethanol. This solution was poured into ice water, collected, and recrystallized three times from carbon tetrachloride, yield 1.5 g (13%), mp 158–160°.

When the residue was not treated with ethanol but recrystallized directly from either chloroform or carbon tetrachloride, a compound mixture resulted, mp 134–136°.

Anal. Calcd for 1:1 **2**-**3**, $C_{16}H_{17}N_2Cl_5O_4$: C, 40.15; H, 3.58; N, 5.85; Cl, 37.04. Found: C, 40.15; H, 3.60; N, 5.62; Cl, 36.96.

This compound mixture was broken up by treating its chloroform solution with a few milliliters of pyridine to obtain **9**, the insoluble pyridinium salt of the chloromethyl compound, mp 230–235° dec. Pure **2** was then obtained by recrystallization from a small amount of chloroform, mp 161–162°.

Anal. Calcd for $C_8H_9NCl_2O_2$: C, 43.26; H, 4.08; N, 6.31; Cl, 31.93. Found: C, 43.31; H, 4.24; N, 6.30; Cl, 31.86.

3,4-Dichloro-2-methylpyrrole (**4**).—Into a 250-ml three-necked flask equipped with a graduated Dean-Stark trap, nitrogen inlet, and stirrer were placed 3.3 g (0.015 mol) of ester **2** and 5 g (0.125 mol) of sodium hydroxide in 175 ml of water. The reaction was boiled under nitrogen for 20 hr. The product appeared after 1 hr and the reaction was about 80% complete after 8 hr. The liquid product was drawn off from the top and weighed, yield 2.0 g (89%), mp 16.0–16.5°, d^{23} 1.27 g/ml.

Pure **4** is a colorless, highly refractive, syrupy liquid possessing a strong characteristic odor somewhat similar to 3,4-dichloropyrrole **7**. Upon brief exposure to atmospheric oxygen, the clear liquid turns brown and then to a black solid. Its dichloromethane solution was stable enough to enter it into the next reaction.

3,4-Dichloro-5-methylpyrrole-2-aldehyde (**5**).—A formylating mixture was prepared by slowly adding 2.5 g (0.0165 mol) of phosphorus oxychloride into 1.2 g (0.0165 mol) of chilled dimethylformamide,[23] and then quickly diluting with 15 ml of methylene chloride. To this well-stirred solution, 2.0 g (0.0135 mol) of **4** in 15 ml of methylene chloride was added at 0° during 15 min. A bright yellow solid separated. The mixture was diluted with 15 ml of methylene chloride, heated for 30 min (hydrogen chloride was evolved), and neutralized with a 20-ml

(18) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(19) G. Mazzara and A. Borgo, *Gazza. Chim. Ital.*, **35**, 104 (1905). The isolated "compound" methyl 3,4-dichloropyrrole-2-carboxylate was later[5] shown to be a 1:1 mixture of the 3,4-dichloro and 4,5-dichloro isomers.

(20) G. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(21) H. Fischer and E. Fink, *Z. Physiol. Chem.*, **283**, 152 (1948).

(22) H. Fischer and E. Fink, *ibid.*, **280**, 123 (1944).

(23) "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 831.

solution of 8.2 g (0.1 mol) of sodium acetate. The mixture was brought to a boil and upon cooling the product separated. It was recrystallized from Skellysolve B containing 5% carbon tetrachloride, yield 2.3 g (96%), mp 169–170°, semicarbazone mp 258° dec.

Anal. Calcd for $C_6H_5NCl_2O$: C, 40.48; H, 2.83; N, 7.87; Cl, 39.83. Found: C, 40.65; H, 2.78; N, 8.02; Cl, 40.14.

5-Bromomethyl-3,4-dichloropyrrole-2-aldehyde (15).—Under illumination from a 150-W frosted lamp, 3.2 g (0.020 mol) of bromine in 5 ml of carbon tetrachloride was added in 15 min to a solution of 3.6 g (0.020 mol) of aldehyde **5** in 120 ml of dry carbon tetrachloride. After refluxing for 15 min, the solvent was removed under vacuum and the residue was recrystallized twice from carbon tetrachloride, yield 1.5 g (29%), mp 147–150° dec with evolution of gas.

Anal. Calcd for $C_6H_4Cl_2BrNO$: C, 28.05; H, 1.57; N, 5.45; Br, 31.11; Cl, 27.60. Found: C, 27.87; H, 1.80; N, 5.34; Br, 30.83; Cl, 27.50.

Ethyl 5-Bromomethyl-3,4-dichloropyrrole-2-carboxylate (16).—A refluxing and illuminated solution of 11.0 g (0.0500 mol) of **2** in 475 ml of dry carbon tetrachloride was treated dropwise with 8.0 g (0.050 mol) of bromine in 10 ml of carbon tetrachloride. The solvent was removed (*in vacuo*) and the residue was recrystallized from carbon tetrachloride, yield 8.3 g (55%), mp 173–174° dec.

Anal. Calcd for $C_8H_8NCl_2BrO_2$: C, 31.92; H, 2.68; N, 4.65; Cl, 23.56; Br, 26.55. Found: C, 31.90; H, 2.93; N, 4.48; Cl, 23.39; Br, 26.39.

Ethyl 3,4-Dichloro-5-chloromethylpyrrole-2-carboxylate (3).—A 400-ml dry ether solution containing 40.0 g (0.261 mol) of **1** was treated dropwise under nitrogen with 110 g (0.811 mol) of sulfuryl chloride. The crystals which separated upon cooling were recrystallized from chloroform, yield 50.5 g (74.8%), mp 158–159° (lit.[2] mp 160–161° with browning).

Ethyl 3,4-Dibromo-5-methylpyrrole-2-carboxylate (25).—To 1.5 g (0.010 mol) of **1** in 80 ml of ether at 3–4° was added dropwise 3.3 g (0.020 mol) of bromine in 10 ml of carbon tetrachloride. The solvents were removed *in vacuo* and the product was recrystallized from 80 ml of carbon tetrachloride, yield 2.5 g (81%), mp 172–174°, (lit.[4] mp 176°).

Anal. Calcd for $C_8H_9NBr_2O_2$: C, 30.89; H, 2.92; N, 4.50; Br, 51.39. Found: C, 30.97; H, 2.99; N, 4.29; Br, 51.31.

Ethyl 3,4-Dibromo-5-bromomethylpyrrole-2-carboxylate (26).—Under illumination, 9.4 g (0.030 mol) of **25** in 250 ml of boiling carbon tetrachloride was treated dropwise with 4.8 g (0.030 mol) of bromine in 20 ml of carbon tetrachloride. White crystals separated upon cooling, yield 8.2 g (69.5%), mp 190–192° dec.

Anal. Calcd for $C_8H_8NBr_3O_2$: C, 24.64; H, 2.07; N, 3.59; Br, 61.49. Found: C, 24.51; H, 2.43; N, 3.51; Br, 60.62.

Compound **26** was also prepared directly from **1** in illuminated and refluxing carbon tetrachloride in 60.8% yield.

Ethyl 3,4-Diiodo-5-methylpyrrole-2-carboxylate (29).—Into an open flask were placed 153 g (0.100 mol) of **1** and a 500-ml solution containing 100 g (1.00 mol) of potassium bicarbonate. The mixture was heated to near boiling and gradually a solution of 76.0 g (0.30 mol) of iodine and 250 g (1.5 mol) of potassium iodide in water was added. Heating was continued for 30 min. The crude product was recrystallized several times from carbon tetrachloride, yield 21.0 g (53%), mp 193–195° and 220° dec.

Anal. Calcd for $C_8H_9NI_2O_2$: C, 23.72; H, 2.24; N, 3.46; I, 62.67. Found: C, 24.57; H, 2.46; N, 3.73; I, 65.16.

Compund **29** was treated with bromine in carbon tetrachloride in an attempt to produce **30**. An immediate violet coloration, indicative of iodine liberation, was observed. No product could be isolated.

Ethyl 3,4-Dichloro-5-hydroxymethylpyrrole-2-carboxylate (19).—A suspension of 6.0 g (0.020 mol) of **16** was refluxed 4 hr in 750 ml of water containing 5 ml of 48% hydrobromic acid. The suspension was filtered hot through a preheated sintered-glass funnel to remove the brownish solids. The clear filtrate yielded 2.3 g (49%) of a lustrous product after recrystallization from chloroform, mp 144–145° (lit.[2] mp 144° obtained from hydrolysis of **3**).

Anal. Calcd for $C_8H_9NCl_2O_3$: C, 40.35; H, 3.81; N, 5.88; Cl, 29.78. Found: C, 40.30; H, 3.88; N, 5.82; Cl, 29.70.

Diethyl 3,3′,4,4′-Tetrachloro-2,2′-dipyrrylmethane-5,5′-dicarboxylate (17). A. From 16.—The dark residue from the above reaction was air-dried and recrystallized from ethylene chloride, chloroform, and again from ethylene chloride. Fine white crystals of **17** containing *ca.* one molecule of solvent were obtained, 2.6 g (53%), mp 212–214° (lit.[2] mp 211°); at 120° a phase change occurs with loss of solvent.

Anal. Calcd for $C_{15}H_{14}N_2Cl_4O_4 \cdot C_2H_4Cl_2$: C, 38.74; H, 3.44; N, 5.32; Cl, 40.36. Found: C, 37.60; H, 3.06; N, 5.28; Cl, 39.26.

A sample of this transparent crystalline compound was heated at 125° for 18 hr and was allowed to cool in air. The resulting free-flowing powder was analyzed.

Anal. Calcd for $C_{15}H_{14}N_2Cl_4O_4 \cdot H_2O$: C, 40.38; H, 3.62; N, 6.28; Cl, 31.79. Found: C, 40.62; H, 3.38; N, 6.35; Cl, 31.84.

When **17** was recrystallized from glacial acetic acid, very fine wooly crystals were obtained containing one molecule of solvent. They are extremely soluble in carbon tetrachloride, chloroform, dichloroethane, and similar solvents.

Anal. Calcd for $C_{15}H_{14}N_2Cl_4O_4 \cdot C_2H_4O_2$: C, 41.82; H, 3.72; N, 5.74; Cl, 29.73. Found: C, 41.96; H, 3.93; N, 5.92; Cl, 29.05.

When 1.0 g (0.0030 mol) of **16** was refluxed 18 hr in glacial acetic acid, 0.60 g of starting material was isolated. Attempted synthesis of **17** in ethanol resulted in an 83% yield of **23**, mp 104–105° (lit.[2] mp 105°).

B. From 3.—A suspension of 85.6 g (0.341 mol) of **3** in 650 ml of water was refluxed for 4 hr. The gray powder obtained was recrystallized once from glacial acetic acid to form the molecular compound of **17** with acetic acid. This solid was extracted with five 100-ml portions of boiling carbon tetrachloride. The insoluble residue was a white powder, 13.7 g (18%), mp 195–197°.

Anal. Calcd for **20**, $C_{16}H_{16}N_2Cl_4O_5$: C, 41.94; H, 3.52; N, 6.12; Cl, 30.96. Found: C, 41.72; H, 3.54; N, 6.13; Cl, 31.15.

Work-up of the combined extractates yielded 18.0 g (25%) of pure **17** complexes with acetic acid. This complex was broken up with solid sodium carbonate.

C. From 19.—When the alcohol **19** was refluxed for 12 hr in water, the starting material was recovered. However, acidification with hydrobromic acid followed by 4 hr of reflux afforded **17** in 40% yield.

3,3′,4,4′-Tetrachloro-2,2′-dipyrrylmethane (13).—After repeated unsuccessful trials it was found that standard decarboxylation procedures including that of Chu and Chu[24] are too extreme because product **13** is too sensitive. A suspension of 2.1 g (0.0050 mol) of diester **17** in a solution of 5.0 g (0.125 mol) of sodium hydroxide in 175 ml of water was refluxed under rigorous exclusion of oxygen and light for 20 hr. The brownish solution was cooled slowly and after 1 hr the powdery product was collected, washed with water, and dried in a stream of nitrogen, yield 1.2 g (86%), mp 111–113°, light sensitive and unstable to storage; **13** is very soluble in halocarbon solvents forming solutions unstable to oxygen.

Anal. Calcd for $C_9H_6N_2Cl_4$: C, 38.06; H, 2.13; N, 9.87; Cl, 49.94. Found: C, 38.22; H, 2.30; N, 10.01; Cl, 49.47.

3,3′,4,4′-Tetrachloro-2,2′-dipyrrylmethane-5,5′-dialdehyde (14). A. From 17 by the McFayden–Stevens Method.[25]—The bishydrazide was prepared by refluxing the diester **17** with a 50–100-fold excess of 85% hydrazine hydrate solution in ethanol for several hours. The yield was about 96%. The bisbenzenesulfonylhydrazide was prepared by treating the bishydrazide with 2 mol of benzenesulfonyl chloride in pyridine overnight.[26] The milky suspension obtained by dilution of the reaction mixture with water was coagulated for filtration by addition of acetic acid. The dried bissulfonylhydrazide was recrystallized from a large volume of 95% ethanol, yield 61%, mp 164–170° (resinifies).

Anal. Calcd for $C_{23}H_{18}N_6Cl_4S_2O_6 \cdot {}^1/_2C_2H_5OH$: C, 40.98; H, 3.01; N, 11.95; S, 9.12. Found: C, 41.22; H, 3.13; N, 12.04; S, 9.13.

A suspension of this bisbenzenesulfonylhydrazide, 17.0 g (0.025 mol), was heated in 300 ml of ethylene glycol to 160°. To this was added at once 30 g (0.27 mol) of sodium carbonate. Brisk evolution of nitrogen accompanied the reaction. After 75 sec, the reaction mixture was quenched with 400 ml of hot water.[26] The aldehyde separated as a nearly colorless powder, yield 4.5 g (53%), darkens at 235° without melting and melts at 300° dec.

(24) T. Chu and E. Chu, *J. Org. Chem.*, **19**, 266 (1954).
(25) E. Mosettig, *Org. React.*, **8**, 232 (1954).
(26) D. Price, E. May, and F. Pickel, *J. Amer. Chem. Soc.*, **62**, 2818 (1939).

Anal. Calcd for $C_{11}H_6N_2Cl_4O_2$: C, 38.85; H, 1.78; N, 8.25; Cl, 41.71. Found: C, 38.99; H, 1.92; N, 8.44; Cl, 41.59.

B. From 13.—In an attempted monoformylation by the Villsmeier method[23] employing 1 mol of dimethylformamide–phosphorus oxychloride complex a nearly quantitative yield of the diformylated product **14** resulted.

C. From 15.—The bromomethylaldehyde **15**, 0.5 g (0.002 mol), was refluxed in water for 17 hr. The products isolated follow: **18**, mp 145–147°, ir 3413 cm^{-1} (OH str, in Nujol); **5**, mp 167–170°, ir identical with ir of authentic sample; impure **14**, melting point and ir spectrum identical with those of compounds prepared above.

Diethyl 3,3′,4,4′-Tetrabromo-2,2′-dipyrrylmethane-5,5′-dicarboxylate (24).—Compound **26** (5 g, 0.0128 mol) was suspended in 600 ml of water; the mixture was refluxed for 2.5 hr. White crystalline material was separated mechanically from the brown lumps and was recrystallized from chloroform, mp 139–141°.

Anal. Calcd for $C_8H_9NBr_2O_3$: C, 29.38; H, 2.77; N, 4.28; Br, 48.87. Found: C, 30.10; H, 2.76; N, 4.29; Br, 50.12.

The brown lumps were recrystallized from glacial acetic acid twice to obtain an analytical sample of **24**, mp 223–225°; solvent evolved at 120°.

Anal. Calcd for $C_{15}H_{14}N_2Br_4O_4 \cdot C_2H_4O_2$: C, 30.66; H, 2.72; N, 4.21; Br, 48.00. Found: C, 30.64; H, 2.52; N, 4.08; Br, 48.62.

In a larger run (4 hr) the ether by-product **28** was isolated and recrystallized from acetic acid, mp 219–221°.

Anal. Calcd for $C_{16}H_{16}N_2Br_4O_5$: C, 30.21; H, 2.54; N, 4.40; Br, 50.26. Found: C, 30.73; H, 3.22; N, 4.32; Br, 49.70.

As in the preparation of **17** the carbon tetrachloride extracts were worked up into ethylene chloride and the acetic acid complex was broken down with solid sodium bicarbonate. The dipyrrylmethane **24** crystallized rapidly from the filtrate, 120° transition, mp 219–221°.

Anal. Calcd for $C_{15}H_{14}N_2Br_4O_4 \cdot {}^1/_2C_2H_4Cl_2$: C, 29.32; H, 2.46; N, 4.27; Br, 48.77; Cl, 5.41. Found: C, 29.37; H, 2.53; N, 4.07; Br, 48.91; Cl, 5.28.

Diethyl 3,4-Dichloropyrrole-2,5-dicarboxylate (6).—An ether solution of 30.6 g (0.200 mol) of **1** was treated dropwise with cooling with 162 g (1.20 mol) of sulfuryl chloride. After 3 hr at room temperature the volatile materials were removed *in vacuo* and the residual oil was refluxed with 400 ml of 95% ethanol for 2 hr. The product **6** was recrystallized once from Skellysolve B, 27.5 g (51.9%), mp 98–106°, which was of sufficient purity for the next step. Repeated recrystallizations from Skellysolve B lowered the yield to 24% and raised the melting point to 112–114° (lit.[2] mp 116°).

3,4-Dichloropyrrole (7).—A silver-lined autoclave[3] was not available and a glass-lined autoclave was found unsuitable. Therefore, a reflux method was developed. Into a 250-ml flask fitted with a stirrer, condenser, and a nitrogen inlet were placed 5.6 g (0.020 mol) of diester **6**, 120 ml of diethylene glycol, and 5.0 g (0.125 mol) of sodium hydroxide in 15 ml of water. The resulting solution was refluxed for 5 hr, cooled, poured into ice, filtered, and extracted with ether. The residue from ether was sublimed, yield 1.20 g (44.1%), mp 73.5–74° (lit.[3] mp 74°).

Anal. Calcd for $C_4H_3NCl_2$: C, 35.33; H, 2.22; N, 10.30; Cl, 52.15. Found: C, 35.22; H, 2.22; N, 10.25; Cl, 52.06.

2,3,4,5-Tetrachloropyrrole.—A solution of 1.36 g (0.0100 mol) of 3,4-dichloropyrrole **7** in 125 ml of ether was treated dropwise (3–5°) with 2.70 g (0.0200 mol) of sulfuryl chloride, and the product was isolated by sublimation at 50° bath temperature, yield 1.85 g (90.2%), mp 107–108° (lit.[4] mp 108°), decomposes on standing.

Anal. Calcd for C_4HNCl_4: C, 23.45; H, 0.49; N, 6.84; Cl, 69.22. Found: C, 23.58; H, 0.56; N, 6.80; Cl, 69.23.

3,4-Dichloropyrrole-2-aldehyde (8).—A methylene chloride solution of 3.4 g (0.025 mol) of 3,4-dichloropyrrole **7** was formylated ($POCl_3$ + DMF) and worked up as described under the preparation of **5**. The essentially pure aldehyde was recrystallized from chloroform, yield 2.8 g (68%), mp 170–172°. The semicarbazone had mp 251° dec; the 2,4-dinitrophenylhydrazone did not melt below 285°.

Anal. Calcd for $C_5H_3NCl_2O$: C, 36.62; H, 1.84; N, 8.54; Cl, 43.24. Found: C, 36.44; H, 2.27; N, 8.40; Cl, 43.30.

3,4-Dichloro-2-iodo-5-methylpyrrole (11).—To a warmed solution of 0.90 g (0.0050 mol) of 3,4-dichloro-5-methylpyrrole-2-carboxylic acid (obtained by alkaline hydrolysis of **2**) containing 2.0 g (0.020 mol) of potassium bicarbonate in 40 ml of water was added a solution of 2.5 g (0.010 mol) of iodine and 6.12 g (0.039 mol) of potassium iodide in 40 ml of water. Addition was stopped when decolorization of iodine ceased. The flask was cooled and the precipitate was sublimed at 50°, yield 1.2 g (86%), mp 81–82° unstable, slightly yellow compound possessing a characteristic odor. This compound decomposes spontaneously to black polymers.

Reduction with Lithium Aluminum Hydride. A. Reduction of 3,4-Dichloropyrrole-2-aldehyde (8).—To a well-stirred, nitrogen-protected mixture of 5.7 g (0.15 mol) of $LiAlH_4$ in 150 ml of absolute ether was added a solution of 16.4 g (0.10 mol) of aldehyde **8** in 1.5 hr. After a 2-hr reflux, water (100 ml) was added cautiously followed by dilute sulfuric acid. The ether layer was separated, washed well (H_2O, $NaHCO_3$ solution, H_2O), and dried over solid sodium sulfate overnight. The ether was removed *in vacuo* and upon warming to room temperature the red oil decomposed to a dark solid and water.

B. Reduction of Diethyl 3,3′,4,4′-Tetrachloridipyrrylmethane-2,2′-dicarboxylate (17).—To a suspension of 1.5 g (0.040 mol) of $LiAlH_4$ in 150 ml of ether was added portionwise 4.28 g (0.0100 mol) of powdered diester **17**. After 1 hr of reflux, the product was worked up as in method A. The product **22** was a reactive, nearly colorless liquid which could not be distilled or chromatogaphically purified without decomposition.

Fluorination of Diethyl 3,4-dichloropyrrole-2,5-dicarboxylate (6). A. Potassium Fluoride.—A solution of 5 g (0.018 mol) of dihalide **6** and 3.0 g (0.05 mol) of anhydrous KF in 50 ml of DMF was refluxed with exclusion of moisture overnight. The solid obtained upon evaporation was recrystallized twice from ethanol, mp 114–116°; mixture melting point with **6** undepressed.

A similar reaction mixture with 1-methyl-2-pyrrolidinone substituted for the solvent was refluxed 36 hr and, after recrystallization from ethanol, the melting point was 115–116°, mixture melting point with **6** undepressed.

B. Arsenic(III) Fluoride.—A 50-ml ethanol solution containing 1.0 g (0.004 mol) of **6** and 0.80 g (0.006 mol) of AsF_3 was refluxed for 3 days. The product was recrystallized from 95% EtOH and melting points and mixture melting points were found undepressed.

C. Antimony(III) Fluoride.—Two days of reflux of **6** with SbF_3 also yielded starting material.

D. Silver(I) Fluoride.—A 50-ml absolute EtOH solution of 6.3 g (0.022 mol) of **6** and 10 g (0.079 mol) of AgF was similarly refluxed, and, upon vacuum sublimation of the precipitate, starting material was formed.

Registry No.—**1**, 3284-51-3; **2**, 24691-21-2; **3**, 24691-22-3; **4**, 24691-23-4; **5**, 24691-24-5; **6**, 24728-04-9; **7**, 1192-19-4; **8**, 24691-26-7; **8** simicarbazone, 24691-27-8; **8** 2,4-dinitrophenylhydrazone, 24691-28-9; **9** Cl, 24691-29-0; **9** Br, 24699-64-7; **10**, 24691-30-3; **11**, 24691-31-4; **13**, 24691-32-5; **14**, 24728-05-0; **15**, 24691-33-6; **16**, 24691-34-7; **17**, 24691-35-8; **17** bisbenzenesulfonylhydrazide, 24691-36-9; **18**, 24691-37-0; **19**, 24691-38-1; **20**, 24728-06-1; **22**, 24691-39-2; **23**, 24691-40-5; **24**, 24691-41-6; **25**, 24728-07-2; **26**, 24691-42-7; **27**, 24691-43-8; **28**, 24691-48-3; **29**, 24691-44-9; **33**, 24691-45-0; **34**, 24691-46-1; 2,5-dicarbethoxy-3,6-dimethylpyrazine, 24691-47-2; 2,3,4,5-tetrachloropyrrole, 24691-49-4.

Alkylations of Heterocyclic Ambident Anions. III.[1] 4-Hydroxypyrimidines[2a]

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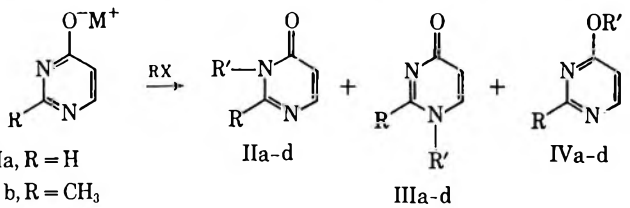
Salts of 4-hydroxypyrimidine and several 2-substituted 4-hydroxypyrimidines were treated with alkyl halides under a variety of reaction conditions. In cation-solvating media, methylation occurred mainly at N-3. Increased N-1 methylation was observed in hydrogen-bonding solvents and solvents of lower dielectric constant. Studies in dimethylformamide revealed significant steric influences. When the alkyl halide was varied from methyl to ethyl to isopropyl or when the group on the 2 position was varied from hydrogen to methyl to ethyl, alkylation at oxygen increased at the expense of alkylation at N-3. 2-Trifluoromethyl-4-hydroxypyrimidine in dimethylformamide reacted with alkyl halides to give mainly 4-alkoxy-2-trifluoromethylpyrimidines.

We have described the effects of alkylating agent, solvent, and cation on the course of alkylation of 2-hydroxypyrimidine[3] and 2-hydroxypyridine salts,[1] and now report on the results of a similar study with 4-hydroxypyrimidine (Ia) and several 2-substituted 4-hydroxypyrimidines (Ib–d).

Reactions of pyrimidines of structure I give both N-alkylation (II + III) and O-alkylation (IV) products. Carbon alkylation of these and related nitrogen heterocycles has not been observed.



Ia, R = H
b, R = CH_3
c, R = C_2H_5
d, R = CF_3

IIa-d

IIIa-d

IVa-d

Results and Discussion

Kornblum has examined the reactions of alkyl halides with silver nitrate and rationalized the changes in product distribution with variation of the alkylating agent by assuming a transition state with both SN1 and SN2 characteristics.[4] In the present study, the sodium salt of 4-hydroxypyrimidine (Ia), 2-methyl-4-hydroxypyrimidine (Ib), and 2-ethyl-4-hydroxypyrimidine (Ic) were alkylated with methyl, ethyl, and isopropyl iodides in methanol. Second-order rate constants were obtained by following the reactions to at least 60% completion (Table I). The rates of alkylation decreased with increasing size of the alkylating agent and of the 2 substituent, also consistent with a bimolecular process.

These observations indicate that, in this series, a changing SN2–SN1 character of the transition state does not play a significant role, and changes in isomer distribution must be due to other factors.

Data in Table II are from studies in dimethylformamide (DMF) and show also that increasing bulk of both the alkylating agent and the substituent in the 2 position favor oxygen alkylation at the expense of N-3. These results are consistent with those obtained under similar circumstances with the salts of 2-pyridones and 2-pyrimidones.[1,3] These results also can be rationalized on the grounds that the rate of nitrogen alkylation is decreased because of steric effects while the rate of oxygen alkylation remains fairly constant, thus leading to exclusive ether formation from the reaction of isopropyl bromide with the sodium salt of 2-ethyl-4-hydroxypyrimidine.

The sodium salt of 2-trifluoromethyl-4-hydroxypyrimidine gives much more O-alkylated product than the other substrates. Electron withdrawal by the trifluoromethyl group would be predicted to reduce the nucleophilicity of the adjacent ring nitrogens to a greater extent than of the "meta" oxygen and, therefore, favors O-alkylation, but steric requirements can-

TABLE I

SECOND-ORDER RATE CONSTANTS[a] FOR ALKYLATIONS OF THE SODIUM SALTS OF 2-SUBSTITUTED 4-HYDROXYPYRIMIDINES (0.45 *M*) IN METHANOL

Alkylating agent	2 substituent H	Me	Et	Temp, °C
MeI	3.34	1.84	1.41	54
EtI	2.28			54
	4.95	3.44	2.61	94
i-PrI	1.70	1.37		94

[a] In l. mol^{-1} sec^{-1} × 10^3.

TABLE II

SODIUM SALT ALKYLATIONS OF 4-HYDROXYPYRIMIDINES AT 40° AND 0.45 *M* IN DMF[a]

Alkylating agent	2 substituent	Yield, %	Product distribution, % O	N-3	N-1
MeI	H	100		82	18
	Me	96		80	20
	Et	82		81	18
	CF_3	100	60	40	
EtBr	H	91	24	66	10
	Me	90	29	50	21
	Et	100	49	38	13
	CF_3	98	100		
i-PrBr[b]	H	96	55	32	13
	Me	46[c]	100		
	Et	60[c]	100		

[a] Over 80% of pyrimidines accounted for as products and/or starting material. [b] Product analysis of the isopropylation reactions are estimates based on the properties of analogous pyrimidines described in this paper. [c] 4-Hydroxypyrimidine was isolated indicating that dehydrobromination of the alkyl halide had occurred.

(1) Part II: G. C. Hopkins, J. P. Jonak, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **32**, 4040 (1967).

(2) (a) This investigation was supported by the Public Health Service Grants No. CA-02857 and CA-10746 from the National Cancer Institute. (b) Allied Chemical Fellow, 1964–1965.

(3) G. C. Hopkins, J. P. Jonak, H. J. Minnemeyer, and H. Tieckelmann, *ibid.*, **31**, 3969 (1966).

(4) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

not be neglected. Della[5] has found that this group has an equatorial preference as great or greater than that of the ethyl group.

When a good cation solvent was used (*e.g.*, DMF, diglyme, methanol), lithium, sodium, and potassium salts of these 4-hydroxypyrimidines all gave essentially the same product distribution. This is expected since the solvent probably insulates the pyrimidine anion from the cation so the effect of the latter is minimal. Experiments under similar conditions have confirmed this in 2-pyridones and 2-pyrimidones.[1,3] However, in ethyl acetate, where the pyrimidine salts were insoluble, the cation did appear to play a role, but no discernible pattern was evident. Studies in this area are continuing.

The alkylation of silver salts of 4-hydroxy- and 2-methyl-4-hydroxypyrimidine in benzene gave products with oxygen to N-3 alkylation ratios of approximately 5:1, but overall yields were low, 20–30%. If a reaction was quenched after only a short period, it was possible to account for 90% of the starting pyrimidine. However, the products were unstable under reaction conditions. Exclusive of some dialkylated materials, attempts at isolation and identification of decomposition products were unsuccessful. Reactions in which the hydroxypyrimidine and silver carbonate were used gave the same results.

Examples are given in Tables III and IV which show product distribution resulting from reaction of the sodium salt of 2-methyl-4-hydroxypyrimidine with methyl iodide in a variety of solvents. As the ionizing power of the reaction medium decreased, N-1 alkylation increased. Similar results were obtained from methylations and ethylations of the sodium salt of 4-hydroxypyrimidine.

A bench-scale reaction of the sodium salt of 4-hydroxypyrimidine with methyl iodide in DMF gave an 80% yield of 3-methyl-4-pyrimidone. When the methylation was performed in refluxing tetrahydrofuran, 1-methyl-4-pyrimidone was isolated in 54% yield after purification.

Reactions run in dimethyl sulfoxide (DMSO) and in methanol were homogeneous from start to finish, while those in DMF were heterogeneous at the start and became homogeneous as the reaction progressed. Reactions in DMF and in DMSO were essentially complete in 5–10 min at room temperature. Reactions in methanol were complete in 1 hr. Generally, reaction mixtures were examined after considerably longer time. Under the conditions studied, products did not equilibrate.

As the dielectric constant of the solvent decreased, the alkali metal salts became more insoluble and the reactions became slower.

Alkylations in solvents such as isopropyl alcohol, *n*-butyl alcohol, and acetone started heterogeneously and, as the reaction proceeded, homogeneity occurred. Alkylations in ethyl acetate were heterogeneous from start to finish.

Kornblum[6] has shown that homogeneity plays an important role in the alkylation of phenoxides. However, when the sodium salt of 4-hydroxypyrimidine was alkylated with ethyl iodide in isopropyl alcohol the product distribution did not vary within experimental error to 72% completion, even though the reaction was heterogeneous at the start and homogeneous after about 40% completion. Table V summarizes the data.

TABLE III

ETHYLATIONS OF THE SODIUM SALT OF 2-METHYL-4-HYDROXYPYRIMIDINE AT 40° AND 0.45 *M* WITH ETHYL BROMIDE

Solvent	Reaction time, hr	Yield, %	Product distribution, % Ether	N-3	N-1
DMF	17	82	29	50	21
MeOH	13	80	25	59	16
i-PrOH	16	104			
	5	84	17	47	36
EtOAc	24	23[a]	5	5	90

[a] 70% sodium salt of 2-methyl-4-hydroxypyrimidine was recovered.

TABLE IV

METHYLATION OF THE SODIUM SALT OF 2-METHYL-4-HYDROXYPYRIMIDINE AT 40° AND 0.45 *M* WITH METHYL IODIDE[a]

Solvent	Reaction time, hr	Yield, %	N-3, %	N-1, %
Formamide[b]	7	86	53	47
Water[b]	2	62	45	55
DMSO	7	76	84	16
DMF	3	96	80	20
MeOH	5	89	66	34
Acetone	11	99	38	62
n-BuOH	8	91	46	54
i-PrOH	8	81	53	47
t-BuOH	60	82	36	64
EtOAc	8	88	12	88
THF	240	47		100

[a] No ether formation was observed. [b] Alkylating agent was insoluble in solvent.

TABLE V

REACTION OF THE SODIUM SALT OF 4-HYDROXYPYRIMIDINE WITH ETHYL IODIDE AT 52° IN ISOPROPYL ALCOHOL

% complete	Product distribution, % Ether	N-3	N-1
10[a]	2	38	60
18[a]	5	42	53
27[a]	4	37	59
33[a]	5	43	52
53[b]	4	42	54
72[b]	4	44	52

[a] Heterogeneous. The first aliquots were difficult to measure accurately because of this heterogeneity. [b] Homogeneous.

The problem of the distribution of negative charge in the 2-pyridone and 2- and 4-pyrimidone anion has not been resolved. On spectroscopic grounds it has been proposed that this charge is located principally on the N-3 or on oxygen.[7–9] Calculations of charge distribution in the 4-pyrimidone anion employing the semi-empirical iterative extended Hückel theory[10] are sum-

(5) E. W. Della, *Tetrahedron Lett.*, No. 28, 3347 (1966).

(6) N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959).

(7) E. Spinner, *J. Chem. Soc.*, 1232 (1960).

(8) Yu. N. Sheinder and Yu. I. Pomerantsev, *Russ. J. Phys. Chem.*, **33**, 174 (1959).

(9) E. Spinner and J. White, *J. Chem. Soc. B*, 966 (1966).

(10) These data were supplied through the courtesy of James Harlos and Dr. George Clarke of our Chemistry Department.

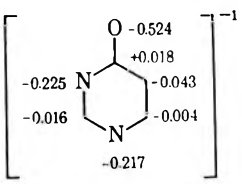
marized in Table VI. The ground-state charge distribution of an isolated ion is shown as structure V. These calculations indicate that approximately 75% of the negative charge in the ion is distributed between the N-3 and the oxygen atom.

TABLE VI

ATOM PARAMETERS USED IN ITERATIVE EXTENDED HÜCKEL TREATMENT OF 4-HYDROXYPYRIMIDINE ANION[11]

	Parameter			
Atom	α_s (eV)	α_p (eV)	$\Delta\alpha$ (eV)	Orbital exponent Z
H	11.6		14.0	1.200
C	25.0	10.0	11.0	1.625
N	30.0	11.5	12.0	1.950
O	33.0	14.0	15.0	2.275

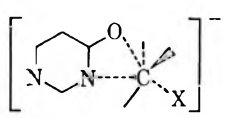
Although the oxygen bears a greater amount of negative charge in the ground state, other factors including the polarizability of the nitrogen atoms must come into play in the transition state to lead to the predominance of nitrogen alkylation (in the absence of steric factors). This is implied by the generalization that alkylating agents carrying little or no charge preferentially form covalent bonds with the more polarizable atom of the ambident systems.[11] Of the atoms under consideration, nitrogen is more polarizable than oxygen, and nitrogen alkylation predominates.



V

In DMF and DMSO, the anion is poorly solvated. It seems reasonable that since approximately 75% of the negative charge is distributed between the N-3 nitrogen and the oxygen atom in the ground state that interaction with the alkylating agent would occur here rather than at N-1. In fact, methylation of the sodium salt of 4-hydroxypyrimidine in DMF leads to 82% N-3 and 17% N-1 isomers.

Brower, Ernst, and Chen[12] have observed in several ambident anion alkylations, including *n*-butylation of the sodium salt of 2-pyridone, that pressure (to 1360 atm) has no effect on product distribution. They concluded from their experiments that "branching of the reactive pathways occurs at or beyond the transition state." By analogy, a transition state as indicated in structure VI involving the "free" pyrimidine anion and



VI

the alkylating agent is consistent with our observations. Since nitrogen is more polarizable, N-C bond formation would be favored.

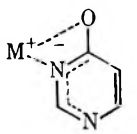
(11) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964).

(12) K. R. Brower, R. L. Ernst, and J. S. Chen, *J. Phys. Chem.*, **68**, 3814 (1964).

The N-3 and O positions are preferentially blocked by hydrogen-bonding solvents and N-1 alkylation becomes more important. When the sodium salt of 4-hydroxypyrimidine reacted with methyl iodide, the amount of N-3 alkylation decreased from 82 to 68 to 59% (N-1 alkylation increased proportionately) in the solvent series DMF, ethanol, and water.

Several reactions were included to determine the effect of concentration on product ratios. The sodium salt of 4-hydroxypyrimidine was alkylated in isopropyl alcohol (0.45 *M*) with ethyl iodide to give N-3 to N-1 product ratio of 46:54. When the concentration was decreased to 0.03 *M*, this ratio became 56:44.[13] These changes are relatively small but the increased alkylation at the N-3 position with decreasing concentration is consistent with the presence of molecular aggregates or ion pairs in solution. Decreasing concentration favors their dissociation, thereby enhancing alkylation of the initially blocked site. Curtin obtains comparable results in the alkylation of 2,6-dimethylphenoxide.[14]

In solvents of lower solvating ability, observations can be rationalized by assuming that in the aggregate the cation blocks the N-3 nitrogen as in structure VII, and, therefore, the N-1 nitrogen can compete effectively.



VII

Leaving groups did not affect the reaction product distribution in good solvation media such as methanol. Only when reactions were run in ethyl acetate with saturated alkylating agents did the leaving group play an important role. The reaction mixtures were heterogeneous from beginning to end. A detailed study of the effect of heterogeneity was not attempted; however, tosylates gave more alkylation at N-3 than did iodides. The data for methylations are presented in Table VII.

TABLE VII

EFFECT OF LEAVING GROUP ON METHYLATION OF 4-HYDROXYPYRIMIDINE IN ETHYL ACETATE (0.45 *M*[a])

Substrate	Cation	Leaving group	% N-3	% N-1
Ia	Li[b]	I	36	64
Ia		OTs	54	46
Ib		I	43	57
Ib		OTs	53	47
Ia	Na[c]	I		100
Ia		OTs	72	28
Ib		I		100
Ib		OTs	25	75
Ia	K[c]	I	57	43
Ia		OTs	83[d]	13
Ib		I	60	40
Ib		OTs	77[e]	16

[a] At least 80% of pyrimidines were recovered in all experiments. [b] 70°. [c] 40°. [d] 4% of ether was isolated. [e] 7% of ether was isolated.

(13) Alkylation of the sodium salt of 4-hydroxypyrimidine with methyl and ethyl iodide in methanol, a good cation solvent, at concentrations of 0.45 and 0.35 *M* produced no variations in isomer distribution.

(14) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Amer. Chem. Soc.*, **80**, 1391 (1958).

Except for decomposition of products at higher temperatures, the variation of temperature (20–90°) had a negligible effect on product distribution. This further supports the premise that branching of the reactive pathway leading to the different isomers occurs after the transition state.

Experimental Section[15]

Methods.—Ultraviolet spectra were determined in aqueous solution on a Perkin-Elmer 202 instrument. Infrared spectra were determined on a Beckman IR-5A spectrophotometer, neat or in a Nujol mull. Nmr spectra were obtained on a Varian A-60 instrument in DMSO-d_6, $CDCl_3$, and D_2O.

Gas chromatograms were obtained on an F & M 720 instrument with column 2 ft in length unless otherwise stated, consisting of 10 or 20% silicon gum rubber on silanized Chromosorb W; the actual pecentage of the silicon gum rubber was not critical. Helium flow rates were 60 ml/min, and runs were programmed from 80–300° at 15°/min. Silica gel was Fisher Certified 100–200 mesh. Alumina was purchased from Woelm and was neutral activity grade I.

General Alkylation Procedure.—The pyrimidine salt alkylating agent[16a] and solvent were sealed in a glass tube and the reaction mixture was maintained at 40 ± 2°. After an appropriate time interval, the reaction mixture was analyzed by gas chromatography to determine the amount of ether, N-3 isomer, and parent hydroxypyrimidine present. Because of its low volatility, the concentration of N-1 isomer was determined by thin layer chromatography on silica gel G containing phosphor G. Separation of all components was accomplished by development with methanol. The pyrimidines were extracted from the silica gel with water. The ultraviolet spectra were determined on the centrifuged supernatant solution. Comparisons with calibrated spectra were reproducible to within ±3%. All compounds were found to be stable under reaction conditions.

The following compounds were prepared according to established procedures: ethyl tosylate,[17] 2-methyl-4-hydroxypyrimidine,[18] 4-hydroxypyrimidine,[19] 2-trifluoromethyl-4-hydroxypyrimidine,[20] 4-methoxypyrimidine,[21] and 4-chloropyrimidine hydrochloride.[22]

Sodium Salt of Ethyl Formylacetate.—A mixture of 125 g (1.69 mol) of ethyl formate and 125 g (1.42 mol) of ethyl acetate was slowly added to a suspension of sodium hydride (62.7 g, 1.42 mol, from a 54.3% mineral oil dispersion from Metal Hydrides, Inc., which was washed with dry ether) in 500 ml of dry ether. Hydrogen evolution ceased about 2 hr after the ester addition was complete. The yellow precipitate was collected and dried *in vacuo* to give 160 g (49%) of product.

This compound was previously prepared in 35% yield by Gabriel[18] using sodium wire. The procedure described above is much simpler and gives purer product in higher yield.

Salts of 4-Hydroxypyrimidines.—Alkali metal salts were prepared from the 4-hydroxypyrimidines and equivalent amounts of the metal or the hydroxide in ethanol or in methanol and dried over phosphorus pentoxide *in vacuo* after removal of solvent. No impurities were detected in nmr spectra where DMSO-d_6 was used as the solvent.

Sodium salts were prepared from sodium ethoxide and an equivalent amount of the hydroxypyrimidine in ethanol. These salts were dried at 100°.

The lithium salt of 2-methyl-4-hydroxypyrimidine was prepared similarly employing lithium metal dissolved in methanol. After evaporation of the solvent, ether was added and evaporated several times to remove methanol. The product was dried at 100°. Lithium hydroxide in a 1:1 solution of methanol and ethanol was added to the pyrimidine in ethanol to form the **lithium salt of 4-hydroxypyrimidine**, which was dried at 140°. Potassium salts were prepared from 87% potassium hydroxide diluted with ethanol. Solvent was evaporated until precipitation occurred. Addition of ether gave a solid which was washed with ether and dried at 100°.

Silver salts were prepared from silver nitrate and the hydroxypyrimidine in water. After neutralization with ammonium hydroxide the precipitates were collected on a centrifuge and washed with water, methanol, and ether.

1-Methyl-4-pyrimidone.—Methyl iodide (12.1 g, 0.0850 mol) was added to a mixture of the sodium salt of 4-hydroxypyrimidine (10.0 g, 0.0850 mol) and 250 ml of tetrahydrofuran. After the mixture was refluxed for 3 days, the solvent was removed *in vacuo*. An ethyl acetate solution of the residue was applied to a silica gel column, and 5.0 g (54%) of product was eluted with absolute ethanol and with methanol, mp 155–156°. This material was identical with an authentic sample prepared by desulfurization of 1-methyl-2-methylthio-4-pyrimidone,[16b] mp 155–156°.

3-Methyl-4-pyrimidone was obtained from 0.41 g (2.92 mmol) of methyl iodide and 0.345 g (2.92 mmol) of the sodium salt of 4-hydroxypyrimidine in 8 ml of dimethylformamide after 2 hr. Evaporation of the solvent and extraction with chloroform gave 0.3 g (94%) of crude product after removal of chloroform. The analytical sample was recrystallized from chloroform: mp 121–122° (lit.[16b] mp 123–124°); uv max (H_2O) 222 mμ (ε 6990), 272 (4000).

1-Ethyl-4-pyrimidone was obtained as a hygroscopic solid by refluxing 5.0 g (43 mmol) of the sodium salt of 4-hydroxypyrimidine and 7.4 g (47 mmol) of ethyl iodide in 120 ml of isopropyl alcohol for 5 hr. After standing for 12 hr the solvent was removed and the product was purified on a silica gel column by eluting with methanol, methanol–ethyl acetate, and ethyl acetate. The analytical sample (1.6 g, 27%) melted at 64–66° and was obtained by recrystallization from acetone–benzene and then from acetone–petroleum ether: uv max (H_2O) 240 mμ (ε 14,600); nmr δ ($CDCl_3$) 1.5 (t, 3 H), 4.1 (q, 2 H), 6.25 (d, 1 H), 7.8 (d, 1 H), and 8.5 (s, 1 H).

Anal. Calcd for $C_6H_8N_2O$: N, 22.56. Found: N, 22.27.

1,2-Dimethyl-4-pyrimidone was obtained from 10.2 g (72.5 mmol) of methyl iodide and 1.2 g (9.0 mmol) of the sodium salt of 2-methyl-4-pyrimidone in 24 ml of ethyl acetate after stirring for 4 days at 50°. After evaporation to dryness the residue was taken up in chloroform and applied to a silica gel column. Elution with methanol and with 95% ethyl alcohol gave 0.3 g (26%) of product: mp 180–182°; uv max (H_2O) 240 mμ (ε 12,605).

Anal. Calcd for $C_6H_8N_2O$: N, 22.56. Found: N, 22.54.

2,3-Dimethyl-4-pyrimidone was obtained from 3.2 g (22 mmol) of methyl iodide and 3.0 g (22 mmol) of the sodium salt of 2-methyl-4-pyrimidone in 50 ml of dimethylformamide after a reaction time of 20 hr. After removal of the solvent the residue was extracted with hot ethyl acetate. The solid which precipitated on cooling was sublimed under reduced pressure to give 0.3 g (27%) of product: mp 63–65°; uv max (H_2O) 222 mμ (ε 4920); nmr δ (D_2O) 2.7 (s, 3 H), 3.6 (s, 3 H), 6.5 (d, 1 H), 7.9 (d, 1 H).

Anal. Calcd for $C_6H_8N_2O$: C, 58.06; H, 6.47. Found: C, 58.51; H, 6.68.

2-Methyl-4-methoxypyrimidine was prepared from 2.1 g (0.0926 g-atom) of sodium in 100 ml of methanol and 5.5 g (33 mmol) of 2-methyl-4-chloropyrimidine hydrochloride[17] by stirring overnight. After removal of the sodium chloride the filtrate was evaporated to give an oil which was extracted with ether. The ether extract was washed with water, dried, and evaporated. The residue was dissolved in benzene and applied to an alumina column and eluted with methylene chloride, chloroform, and ethyl acetate to give 2 g (35%) of product: uv max (H_2O) 212, 251 mμ (ε 3740); nmr δ ($CDCl_3$) 2.6 (s, 3 H), 4.0 (s, 3 H), 6.5 (d, 1 H), 8.35 (d, 1 H).

Anal. Calcd for $C_6H_8N_2O$: N, 22.56. Found: N, 22.30.

(15) Melting points were taken on either a Mel-Temp or a Fisher-Johns apparatus and are corrected. Boiling points are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt, Mülheim, Germany.

(16) (a) Initial methylations of the sodium salt of 4-hydroxypyrimidine were conducted with an excess of methyl iodide. Yields were found to be low and a corresponding amount of an unexpected material was isolated from the reaction mixture. The physical and chemical properties of this compound were identical with those reported by Brown, *et al.*,[16b] for 1,3-dimethyl-4-oxopyrimidinium iodide. Hence, all reactions reported in this paper were run with an equivalent amount of alkylating agent. Excess reagent has been shown to be detrimental also for alkylations of 2-hydroxypyridines with methyl iodide.[4] (b) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 211 (1955).

(17) S. Tipson, *J. Org. Chem.*, **21**, 133 (1947).

(18) S. Gabriel, *Ber.*, **37**, 3638 (1904).

(19) D. J. Brown, *J. Soc. Chem. Ind., London*, **69**, 353 (1950).

(20) S. Inoue, A. J. Saggiomo, and E. A. Nodiff, *J. Org. Chem.*, **26**, 4504 (1961).

(21) D. J. Brown and L. N. Short, *J. Chem. Soc.*, 331 (1953).

(22) M. Boarland and J. McOmie, *ibid.*, 1218 (1951).

2-Methyl-4-ethoxypyrimidine was prepared from 1.62 g (9.8 mmol) of 2-methyl-4-chloropyrimidine hydrochloride[17] and 0.45 g (20 mg-atom) of sodium in 100 ml of absolute ethanol. After 10 hr the sodium chloride was separated and the solvent was removed. The liquid residue was dissolved in ether and collected by gas chromatography: uv max (H_2O) 212, 251 mμ (ε 4160); nmr δ ($CDCl_3$) 1.45 (t, 3 H), 2.65 (s, 3 H), 4.5 (q, 2 H), 6.6 (d, 1 H), 8.4 (d, 1 H).

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30. Found: C, 60.66; H, 7.46.

2-Ethyl-4-ethoxypyrimidine was prepared from 0.36 g (3.3 mmol) of ethyl bromide and 0.50 g (3.4 mmol) of the sodium salt of 2-ethyl-4-pyrimidone in 7.5 ml of DMF. After stirring for 12 hr the liquid product was collected by gas chromatography: uv max (H_2O) 212, 251 mμ; ir (no carbonyl).

Anal. Calcd for $C_8H_{12}N_2O$: C, 63.16; H, 7.89. Found: C, 62.87; H, 8.07.

2-Trifluoromethyl-4-ethoxypyrimidine was prepared from 0.380 g (3.49 mmol) of ethyl bromide and 0.38 g (2.08 mmol) of the sodium salt of 2-trifluoromethyl-4-pyrimidone in 4 ml of dimethylformamide. After stirring 5 hr the solvent was removed under a stream of nitrogen and ether was added. After separation of the sodium bromide and evaporation of most of the solvent, the liquid product was collected by gas chromatography using a 10-ft column: uv max (H_2O) 219, 251.5 mμ; ir (no carbonyl).

Anal. Calcd for $C_7H_7F_3N_2O$: C, 43.77; H, 3.64. Found: C, 44.12; H, 3.90.

Using this procedure, 0.52 g (3.69 mmol) of methyl iodide and 0.39 g (2.1 mmol) of the sodium salt of 2-trifluoromethyl-4-pyrimidone in 4 ml of dimethylformamide gave two liquid products when collected by gas chromatography. 2-Trifluoromethyl-4-methoxypyrimidine had the lower retention time; uv max (H_2O) 218, 250 mμ; ir (neat, no carbonyl).

Anal. Calcd for $C_6H_5F_3N_2O$: C, 40.46; H, 2.83. Found: C, 40.16; H, 3.09.

2-Trifluoromethyl-3-methyl-4-pyrimidone: uv max (H_2O) 224, 279 mμ; ir 5.90 μ (C=O).

Anal. Calcd for $C_6H_5F_3N_2O$: C, 40.46; H, 2.83. Found: C, 40.61; H, 2.98.

3-Ethyl-4-pyrimidone was prepared from 0.168 g (1.42 mmol) of the sodium salt of 4-pyrimidone and 0.215 (1.97 mmol) of ethyl bromide in 4 ml of methanol. After 4 days at 40° the mixture was concentrated by evaporation and the product was collected by gas chromatography: uv max (H_2O) 220, 271 mμ, ir 5.99 μ (C=O); δ (D_2O) 1.5 (t, 3 H), 4.2 (q, 2 H), 6.71 (d, 1 H), 8.2 (broad s, 1 H), 8.7 (broad s, 1 H).

Anal. Calcd for $C_6H_8N_2O$: C, 58.10; H, 6.45. Found: C, 58.60; H, 6.75.

This compound was formed in 33% yield from 3.0 g (25 mmol) of the sodium salt and 3.0 g (29 mmol) of ethyl bromide. After 36 hr the hygroscopic solid was recrystallized from benzene and washed with acetone: mp 70.0–71.5°; uv max (H_2O) 222 mμ (ε 7080), 272 (4060).

4-Ethoxypyrimidine.—A solution of sodium ethoxide, prepared from 0.55 g (24 mg-atom) of sodium and 50 ml of absolute ethanol, was added to a mixture of 1.81 g (12.0 mmol) of 4-chloropyrimidine hydrochloride and 50 ml of absolute ethanol. The reaction mixture was stirred overnight at room temperature. Sodium chloride was removed by filtration, and the filtrate was evaporated *in vacuo* to an oil. Water was added and the mixture was extracted several times with ether. The combined extracts were washed with water, dried over magnesium sulfate, and filtered. The solvent was evaporated *in vacuo* to give an oil which was collected by gas chromatography: uv max (H_2O) 250 mμ (ε 3638); ir (no carbonyl).

Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.49. Found: C, 57.94; H, 6.45.

1-Ethyl-2-methyl-4-pyrimidone.—2-Methyl-4-hydroxypyrimidine (5.0 g, 45 mmol) was mixed with 50 ml of absolute ethanol. A solution of 3.31 g (50 mmol) of 85% potassium hydroxide dissolved in 50 ml of ethanol and 5.9 g (54 mmol) of ethyl bromide was added. The reaction mixture was stirred at room temperature for 1 hr, refluxed for 2 hr, and filtered. The filtrate was evaporated to dryness, and the residue was triturated with hot ethyl acetate and applied to a silica gel column. Elution with absolute ethanol gave fractions with uv max at 225 and 268 mμ. Elution with methanol gave a material absorbing at 240 mμ (ε 14,550). The latter fractions were recrystallized from benzene to give 0.10 g (1.5%) of the desired compound: mp 129–130°; ir 6.1 μ (C=O); δ (D_2O) 1.4 (t, 3 H), 2.6 (s, 3 H), 4.1 (q, 2 H), 6.35 (d, 1 H), 7.85 (d, 1 H).

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.81; H, 7.23; N, 20.18.

2-Methyl-3-ethyl-4-pyrimidone.—A mixture of 3.0 g (23 mmol) of the sodium salt of 2-methyl-4-hydroxypyrimidine, 2.13 g (19.5 mmol) of ethyl bromide, and 50 ml of DMF was stirred overnight at room temperature. The solvent was removed *in vacuo* to give 5.7 g of crude product which was chromatographed initially on alumina with methylene chloride and ethyl acetate and then on silica gel with methylene chloride, ethyl acetate, and methanol to give 0.7 g (22%) of hydroscopic product: mp 44–45°; uv max (H_2O) 223, 273 mμ (ε 4685); nmr δ ($CDCl_3$) 1.35 (t, 3 H), 2.6 (s, 3 H), 4.1 (q, 2 H), 6.3 (d, 1 H), 7.75 (d, 1 H).

Anal. Calcd for $C_7H_{10}N_2O$: N, 20.27. Found: N, 19.93.

2-Ethyl-4-hydroxypyrimidine.—The sodium salt of ethyl formylacetate (100 g, 0.725 mol) was dissolved in 500 ml of water. Propionamidine hydrochloride (44.4 g, 0.408 mol) was added to this solution. The reaction mixture was stirred at room temperature for 3 days and then extracted with ether. The solution was neutralized with hydrochloric acid and the solvent was removed under reduced pressure. The product was obtained by continuous extraction of the residue with absolute ethanol. Evaporation of the ethanol and recrystallization from high-boiling petroleum ether gave 25.1 g (36%), mp 118.5–120.5°. The analytical sample was purified further by double sublimation *in vacuo*: uv max (H_2O) 224 mμ (ε 7280); nmr δ (D_2O) 1.3 (t, 3 H), 2.8 (q, 2 H), 6.45 (d, 1 H), 8.0 (d, 1 H).

Anal. Calcd for $C_6H_8N_2O$: C, 58.06; H, 6.45; N, 22.58. Found: C, 57.85; H, 6.64; N, 22.46.

2,3-Diethyl-4-pyrimidone.—Ethyl bromide (3.57 g 32.8 mmol) was added to a mixture of the sodium salt of 2-ethyl-4-hydroxypyrimidine (5.0 g, 34 mmol) and 75 ml of DMF. After 2 days, the solvent was removed under reduced pressure and the residue was triturated with ethyl acetate. The solution was eluted on a silica gel column successively with methylene chloride, chloroform, ethyl acetate, and methanol. The first methanol fractions yielded the desired N-3 compound as an oil. The yield was 2.6 g (52%): uv max (H_2O) 222 mμ (ε 5300), 273 (4582); nmr δ ($CDCl_3$) 1.3 (t, 6 H), 2.85 (q, 2 H), 4.2 (q, 2 H), 6.35 (d, 1 H), 7.85 (d, 1 H).

Anal. Calcd for $C_8H_{12}N_2O$: N, 18.40. Found: N, 18.25.

1,2-Diethyl-4-pyrimidone.—The latter methanol fractions from the preparation of the 2,3-diethyl-4-pyrimidone gave about 0.3 g (27%) of the N-1 isomer: mp 108–111°; uv max (H_2O) 240 mμ (ε 13,580); nmr δ ($CDCl_3$) 1.25 (m, 6 H), 2.6 (q, 2 H), 3.7 (q, 2 H), 6.0 (d, 1 H), 7.0 (d, 1 H).

Anal. Calcd for $C_8H_{12}N_2O$: N, 18.40. Found: N, 18.09.

Registry No.—1-Ethyl-4-pyrimidone, 6146-20-9; 1,2-dimethyl-4-pyrimidone, 24903-63-7; 2,3-dimethyl-4-pyrimidone, 17758-38-2; 2-methyl-4-methoxypyrimidine, 7314-65-0; 2-methyl-4-ethoxypyrimidine, 24903-66-0; 2-ethyl-4-ethoxypyrimidine, 24903-67-1; 2-trifluoromethyl-4-ethoxypyrimidine, 24903-68-2; 2-trifluoromethyl-4-methoxypyrimidine, 24903-69-3; 2-trifluoromethyl-3-methyl-4-pyrimidone, 24903-70-6; 3-ethyl-4-pyrimidone, 6146-22-1; 4-ethoxypyrimidine, 24903-72-8; 1-ethyl-2-methyl-4-pyrimidone, 24903-73-9; 2-methyl-3-ethyl-4-pyrimidone, 24903-74-0; 2-ethyl-4-hydroxypyrimidine, 24903-75-1; 2,3-diethyl-4-pyrimidone, 24903-76-2; 1,2-diethyl-4-pyrimidone, 24903-77-3; 2-methyl-4-hydroxypyrimidine (sodium salt), 24903-78-4; 4-hydroxypyrimidine (sodium salt), 24903-79-5.

Alkylations of Heterocyclic Ambident Anions. IV. Alkylation of 5-Carbethoxy- and 5-Nitro-2-pyridone Salts[1]

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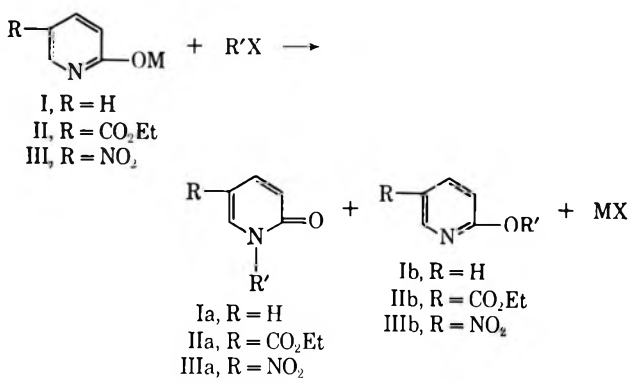
Electron-withdrawing groups on the 5 position of 2-pyridone caused increased N-alkylation. The effect was more pronounced with silver salts than with sodium salts. Only small solvent or cation effects were observed for alkali metal salts. Silver salts gave more O-alkylation than did alkali metal salts but were subject to a solvent effect. Alkylations of silver salts under heterogeneous conditions were slow and gave only O-alkylation.

The conclusion that alkali metal salts of 2-pyridone are predominantly alkylated at nitrogen and that silver salts give increased amounts of oxygen-alkylated product is based on preparative experiments from several laboratories where detailed product analyses were not attempted.[2] Data to evaluate the effect of substituents on alkylations are also limited. However, available evidence indicates that substituents on the 5 position (*para* to the hydroxy group) do not effect product distribution.[2]

In recent studies it was observed that heterogeneity of the reaction medium was probably a determining factor for the site of alkylation of 2-pyridone[3] and 2-pyrimidones.[4] The present paper reports on a study where the cation and solvent were varied in alkylations of salts of 2-hydroxypyridine (I), 2-hydroxy-5-carbethoxypyridine (II), and 2-hydroxy-5-nitropyridine (III)[5] with halides and tosylates.



Results and Discussion

Effect of Alkylating Agents.—The data from alkylations of the sodium salts of the 2-hydroxypyridines I, II, and III in dimethylformamide at ambient temperatures are summarized in Table I. The increase in ether formation, when the alkylating agent was changed from methyl to ethyl to isopropyl halide had been observed previously in alkylations of 2-hydroxypyridine[3] and 2-hydroxypyrimidine,[4] and demonstrates that nitrogen alkylation has a greater steric requirement than does oxygen alkylation. In addition, as the group at the 5 position of the ring was varied from hydrogen to carbethoxy to nitro, alkylation at nitrogen increased. This relatively small but real effect of substituents was observed in alkylations with ethyl and isopropyl halides, where unsubstituted 2-hydroxypyridine (I) gave significant amounts of O-alkylation product.

TABLE I

EFFECTS OF ALKYLATING AGENTS ON THE ALKYLATION OF SODIUM SALTS IN DIMETHYLFORMAMIDE AT ROOM TEMPERATURE[a]

Substrate	Alkyl halide[b]	% yield[c]	Product distribution N	O	P[d]
I	MeI[e]	93	95	5	
	EtI[e]	87	69	31	
	i-PrI[e]	90	30	61	9
	$PhCH_2I$[e]	99	98	2	
II	MeI	68	100		
	EtI	73	78	22	
	i-PrI	84	42	51	7
	$PhCH_2I$	84	98	2	
III	MeI	100	99	1	
	EtI	100	89	11	
	EtOTs	90	78	22	
	i-PrI	82	54	46	
	i-PrOTs	71	47	53	
	$PhCH_2I$	85	96	4	

[a] Alkylations were completed in 24 hr. The analyses were done after 5 days. No O–N isomerization was observed. [b] Reactions were conducted with 200% excess alkyl halides. In benzylation, only 50% excess halide was used. [c] Determined by quantitative vapor phase chromatography. [d] Regenerated hydroxypyridine from elimination reaction. [e] Reference 3.

Several reactions of the sodium salt of III with alkyl halides were studied at elevated temperature (64°). No change in the products ratio was observed in methylations and ethylations. When isopropylation was carried out at 64°, a decrease in yield of ether was observed accompanied by the regeneration of III, indicative of dehydrohalogenation.

Effect of Cation.—Similar N- to O-product ratios were obtained from alkylations of sodium, potassium, or lithium salts. The rates of alkylation of lithium salts were slower than those of sodium and potassium salts. No change in product distribution was observed when the leaving group was varied from chloride to bromide to iodide. Generally, a higher yield was obtained when the alkyl bromide was used.

In dimethylformamide the silver salts of 2-hydroxypyridines or the free acid with silver carbonate gave more O-alkylation when compared with sodium salts. In the alkylations of the silver salt I in dimethylform-

(1) This investigation was supported by Public Health Service Research Grant No. CA-02857 and Grant No. CA-10746 from the National Cancer Institute.

(2) For a recent review of pyridine alkylations, see H. Meislich, "Pyridine and Its Derivatives," Part II, E. Klingsberg, Ed., Interscience Publishers, New York, N. Y., 1962, pp 631–640.

(3) G. C. Hopkins, J. P. Jonak, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **32**, 4040 (1967).

(4) G. C. Hopkins, J. P. Jonak, H. Tieckelmann, and H. J. Minnemeyer, *ibid.*, **31**, 3969 (1966).

(5) The term hydroxypyridine is simply a nomenclature convenience and does not refer to the predominant tautomeric form.

amide, 2-pyridone was regenerated in quantity and, therefore, it was difficult to compare with silver salts of II and III in this solvent. However, the effect of substituents was generally in the same direction as that observed for alkylations of sodium salts but was more pronounced. N-ethylation of sodium salts increased from 69 to 79 to 89% as the hydroxypyridine was varied from I to II to III, but with the corresponding silver salts, N-ethylation increased from 21 to 66 to 91% (Table II).

TABLE II

EFFECTS OF ALKYLATING AGENTS ON THE ALKYLATION OF SILVER SALTS IN DIMETHYLFORMAMIDE AT ROOM TEMPERATURE[a]

Substrate	Alkyl halide[b]	% yield	Product distribution N	O	P[c]
I	MeI[d]	81	73	12	14
	EtI	76	21	40	39
	i-PrBr[d]	No alkylation. Only 2-pyridone was formed.			
	$PhCH_2Br$[d]	85	54	46	
II	MeI	73	96	4	
	EtI	85	66	34	
	i-PrI	94	20	75	5
	$PhCH_2I$	78	89	11	
III	MeI	62	88	12	
	EtI	52	91	9	
	i-PrI	49	36	64	
	$PhCH_2I$	46	96	4	
	MeI[e]	100	88	12	
	EtI[e]	100	83	17	
	i-PrI[e]	100	38	62	

[a] The analyses were performed after 5 days. [b] A 200% excess of alkyl halides was used. In benzylations, a 50% excess of halide was used. [c] Regenerated 2-hydroxypyridines. [d] Reference 3. [e] Silver carbonate and 2-hydroxy-5-nitropyridine were used in place of the isolated salt.

The silver salts were not soluble in dimethylformamide. All of the reaction mixtures were heterogeneous in the beginning but became homogeneous as the reactions proceeded despite the low solubility product of silver iodide in dimethylformamide (3.65×10^{-17} $mol^2/l.^2$).[6]

When the alkylating agent was varied from a 5% to a 200% excess (in DMF) yields from methylations and ethylation of I, II, and III improved with excess alkylating agent. When an excess of isopropyl halide was used with silver salts, a large quantity of 2-pyridone was regenerated. In contrast, when sodium salts were used the yield was increased slightly with an excess of isopropyl halide.

Solvent Effects.—Solvent effects on product distribution in alkylations of sodium salts were small. However, rates of reactions were solvent dependent.

Alkylations of sodium salts of I, II, and III with methyl iodide resulted in greater than 95% nitrogen alkylation in all solvents used (dimethyl sulfoxide, acetonitrile, dimethylformamide, ethyl alcohol, acetone, diglyme, and ethyl acetate). With ethyl iodide, N-alkylation of II varied from 78 to 94%. This relatively small solvent effect is consistent with a reaction which proceeds through a transition state which gives both the O- and the N-alkylated product.[7]

Reactions in dimethylformamide, dimethyl sulfoxide, methanol, or ethanol were homogeneous and proceeded at reasonable rates. Generally, the solubility of sodium salts decreased as the dielectric constant decreased. Reactions did not occur with suspensions in nonpolar solvents such as benzene, *n*-hexane, and tetrahydrofuran.

Contrary to the observations with alkali metal salts, the site of alkylation of silver salts was strongly solvent dependent (Table III). The silver salt of II gave 96% N-methylation in dimethylformamide and only 2% when hexane was used. In all alkylations of silver salts the reaction mixtures were heterogeneous in the early stages of the reaction.

TABLE III

SOLVENT EFFECTS ON ALKYLATION OF THE SILVER SALTS AT ROOM TEMPERATURE[a,b]

Substrate	Alkyl halide	Solvent	% yield	Product distribution N	O	P[c]
I	EtI	DMF	76	21	40	39
		Ether[d]	93	1	96	3
II	MeI	DMF	73	96	4	
		DMF–H_2O	69	68	32	
		MeOH	85	20	80	
		Ether	100	8	92	
		Benzene	93	5	95	
		Hexane	87	2	98	
II	EtI	MeCN	97	5	92	3
		DMF	85	66	34	
		DMF–H_2O	70	12	70	18
		MeOH	79	16	84	
		Acetone	100	8	92	
		Ether	62		100	
		Benzene	100		100	
		Hexane	97	2	98	
III	EtI	DMF	52	91	9	
		MeOH	31	53	47	
		Benzene	71	12	88	
		Hexane	62	10	90	

[a] For reactions in DMF, the analyses were performed after 5 days. For reactions in other solvents the reaction time was 10 days. [b] Alkylating agent was used in 200% excess. [c] 2-hydroxypyridine derivatives. [d] Reference 3.

When hexane, benzene, and ether were used as solvent, the pyridone silver salts and the products were essentially all in the solid phase throughout the reaction and almost exclusive O-alkylation was observed. The rate of alkylation was very slow. When 200% excess of alkyl halide was used, only 10% products were obtained after 12 hr at ambient temperatures. After 10 days, the yield was more than 95% O-alkylated products for all alkyl halides used.

When dimethylformamide was used as the solvent in a methylation of the silver salt of II, only 4% of the product was the methyl ether, but, when a 1:1 ratio (by volume) of dimethylformamide and water was used, the ether product increased to 32%. Similar results were obtained in ethylations and isopropylations. Alkylation of the silver salt of II in acetonitrile (ϵ 38.8)

(6) H. Chateau and M. C. Moncet, *J. Chim. Phys.*, **60**, 1060 (1963).

(7) K. B. Brower, R. L. Ernst, and J. S. Chen, *J. Phys. Chem.*, **68**, 3814 (1964).

gave much more ether than alkylations in dimethylformamide (ϵ 36).

Silver salts form soluble complexes in dimethylformamide. In one experiment the ethylation of silver salts of II in this solvent was followed from start to completion (Table IV). After an induction period, the reaction rate increased dramatically and the solution became homogeneous after 6 hr. The N-ethyl-2-pyridone to 2-ethoxypyridine product ratio was the same throughout the reaction. In another experiment the reaction was stopped when it was approximately one-half completed. The precipitate was filtered and washed with fresh dimethylformamide and benzene to give silver iodide in much less than theoretical yield (20%). The silver salt of II was not detected in the precipitate.

TABLE IV

REACTION OF THE ETHYL IODIDE WITH THE SILVER SALT OF II IN DIMETHYLFORMAMIDE AT ROOM TEMPERATURE

Time, min	% completion	Product distribution N	O
30	4.7		
60	21.5	70	30
80	46	69	31
100	74	68	32
400[a]	77	68	32

[a] The mixture was homogeneous after 400 min.

These observations have demonstrated that alkylations of silver salts in dimethylformamide were homogeneous reactions which gave both the N- and O-alkylated products and that generally the product distribution in homogeneous reactions is solvent dependent. In contrast, reactions of the silver salt in hexane and benzene were heterogeneous and gave exclusive O-alkylation.

Experimental Section

Materials.—All solvents and alkylating agents were reagent grade and usually stored over Linde Molecular Sieves. Additional purification, when necessary, was carried out by standard methods. The salts of 2-hydroxypyridine and its derivatives were obtained according to the method reported.[3] 2-Hydroxypyridine-5-carboxylic acid and 2-hydroxy-5-nitropyridine were obtained from Aldrich Company. Potassium and silver salts of 2-hydroxy-5-nitropyridine, 1-methyl-, 1-ethyl-, 1-isopropyl-, and 1-benzyl-5-nitro-2-pyridone, and 1-methyl-5-carbethoxy-2-pyridone are prepared according to the known procedure.[8,9]

Vapor Phase Chromatography.—The reaction mixtures were analyzed on a F & M Model 720 gas chromatograph. For derivatives of 2-hydroxypyridine, a 2-ft stainless steel column packed with 10% XF-1150 on silanized Chromosorb W was used. The helium flow was 90 ml/min and the temperature was programmed at 15°/min from 100 to 240°. For the derivatives of 2-hydroxy-5-nitropyridine and 2-hydroxy-5-carbethoxypyridine, a 2-ft stainless steel column packed with 10% silicon gum rubber (SE-30) on silanized Chromosorb W was used. The helium flow was 110 ml/min and the temperature was programmed at 15°/min from 110 to 260°. All quantitative analysis data were obtained by comparison with a calibration plot of weighed sample *vs.* peak area.

Alkylation Procedures.—Hydroxypyridine or the salt (0.50–1.00 mmol) was weighed in a small glass vial and usually 2 ml of solvent was added. A suitable amount of alkyl halide was added below the surface with a 100-μl. syringe. The reaction mixture, in a stoppered glass vial, was placed on a shaker. After an appropriate reaction period, 10–40-μl. samples were taken and subjected to vpc analysis.

2-Hydroxy-5-carbethoxypyridine.—Rath[8] reported that, by bubbling hydrogen chloride into the solution of 2-hydroxypyridine-5-carboxylic acid and ethanol, the corresponding ethyl ester could be obtained in 65% yield. In the present preparation, sulfuric acid was used. The product was isolated in 78% yield. After recrystallization from ethyl acetate, the melting point was 151.0–151.5° (lit.[9] 150°).

Sodium Salt of 2-Hydroxy-5-carbethoxypyridine.—Freshly cut sodium (2.3 g, 0.1 g-atom) dissolved in 100 ml of ethanol was added to the solution of II (16.7 g, 0.1 mol) suspended in 100 ml of absolute ethanol. After stirring at room temperature overnight, the solvent was removed under reduced pressure and anhydrous ether was added in large excess. After filtration, the sodium salt was obtained as white crystals, yield 18 g (95%). Titrated by standardized hydrochloric acid, the purity of this salt was 99.9%.

Potassium Salt of 2-Hydroxy-5-carbethoxypyridine.—This compound was prepared by the method which was used for the sodium salt with the exception that potassium hydroxide was used in place of freshly cut sodium. After the work-up procedure, the potassium salt which was analyzed for two molecules of water of crystallization was obtained, yield 16 g (99%). The anhydrous potassium salt was obtained after heating the salt at 50–55° at reduced pressure.

Silver Salt of 2-Hydroxy-5-carbethoxypyridine.—Silver nitrate (25.5 g, 0.15 mol) in 50 ml of water was added to II (16.7 g, 0.1 mol) suspended in 120 ml of water. After the reaction mixture stood in the dark overnight, it was neutralized with 50% ammonium hydroxide (about 15 ml). The white precipitate was centrifuged, was washed with water, ethanol, and ether, and was dried under vacuum, yield 22.2 g (81%). By using Volhard titration method[10] with ferric alum as indicator, it was found that this salt was at least 99% pure.

2-Methoxy-5-carbethoxypyridine.—Silver carbonate (11.9 g, 0.04 mol) and II (6.7 g, 0.04 mol) reacted with methyl iodide (20.5 g, 0.14 mol) for 36 hr in 60 ml of benzene at room temperature in the dark. The reaction mixture was cooled and filtered. The filtrate was washed with 30 ml of 10% sodium bicarbonate solution and then washed twice with 30 ml of water. The benzene solution was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. After steam distillation, the distillate was extracted with 30 ml of chloroform three times. The chloroform was then removed under reduced pressure and a pale yellow color liquid was obtained, yield 3.9 g (51%). The analytical sample was collected from gas chromatography.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.65; H, 6.13; N, 7.73. Found: C, 59.63; H, 6.31; N, 7.55.

2-Ethoxy- and 2-Isopropyloxy-5-carbethoxypyridine.—The method used for these preparations was the same as that used for the 2-methoxy derivative. 2-Ethoxy derivative was isolated in 70% yield, bp 125–129° (0.7 mm).

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.51; H, 6.85; N, 7.18. Found: C, 61.87; H, 7.09; N, 7.33.

2-Isopropyloxy-5-carbethoxypyridine was isolated in 77% yield.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 61.13; H, 7.24; N, 6.69. Found: C, 63.06; H, 7.47; N, 6.94.

2-Benzyloxy-5-carbethoxypyridine.—The procedure used for the preparation of the 2-methoxy derivative was used here with the exception that the isolated silver salt of II was used in place of silver carbonate. The product was isolated in 75% yield before recrystallization. After recrystallization from ligroin (bp 63–75°), the melting point was 50–51°.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.01; H, 5.89; N, 5.45. Found: C, 70.31; H, 5.92; N, 5.46.

1-Ethyl-5-carbethoxy-2-pyridone.—Potassium hydroxide (3 g, .054 mol) in 40 ml of absolute ethanol was added slowly to the solution of II (8 g, 0.048 mol) in 100 ml of absolute ethanol. Ethyl iodide (10 g, 0.064 mol) was then added. After refluxing the reaction mixture for 2.5 hr, the solvent was removed under reduced pressure and the residue was extracted with large amounts of ether. After removing ether at reduced pressure and by steam distillation, the residue was extracted with 30 ml of chloroform three times. The chloroform layer was washed with 50 ml of 25% ammonium hydroxide to remove unreacted II and then washed twice with 100 ml of water. After drying over

(8) C. Rath, *Justus Liebigs Ann. Chem.*, **484**, 52 (1930).
(9) A. Bing and C. Rath, *ibid.*, **487**, 127 (1931).
(10) R. A. Day and A. L. Underwood, "Quantitative Analysis," Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1958, pp 102–106.

magnesium sulfate the solvent was evaporated, yield 5.5 g (59%), bp 130° (0.7 mm).

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.51; H, 6.85; N, 7.18. Found: C, 61.44; H, 6.80; N, 7.08.

1-Isopropyl- and 1-Benzyl-5-carbethoxy-2-pyridones.—The procedure used for the preparation of 1-ethyl-5-carbethoxy-2-pyridone was used with the exception that the potassium salt of II was used. For 1-isopropyl-5-carbethoxy-2-pyridone, after recrystallization from ligroin (bp 63–75°), the yield was 37%, mp 91–92°.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.16; H, 7.24; N, 6.69. Found: C, 63.35; H, 7.47; N, 6.48.

For **1-benzyl-5-carbethoxy-2-pyridone**, the yield was 47%, mp 60.0–60.5°.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.01; H, 5.89; N, 5.45. Found: C, 70.03; H, 5.89; N, 5.60.

Sodium Salt of 2-Hydroxy-5-nitropyridine.—The procedure used for the preparation of sodium salt of II was employed. The yield was 86%.

2-Methoxy-5-nitropyridine.—A cold solution of freshly cut sodium (1.45 g, 0.063 mol) in 50 ml of methanol was added slowly to the solution of 2-chloro-5-nitropyridine (10 g, 0.063 mol) in 150 ml of methanol with stirring and continued cooling. After warming to room temperature, the reaction mixture was allowed to stand overnight with stirring. Solvent was removed *in vacuo* and the residue was extracted with 50 ml of chloroform three times. The chloroform was then washed with two 25-ml portions of water and the solvent was removed under reduced pressure. The product was recrystallized from ethanol, yield 9.4 g (90%), mp 108.0–108.5° (lit.[8] 108–109°).

2-Ethoxy- and 2-Benzyloxy-5-nitropyridine.—These compounds were prepared by the method used for 2-methoxy-5-nitropyridine. The 2-ethoxy-5-nitropyridine was obtained in 98% yield, mp 90–91° (lit.[8] 91–92°). 2-Benzyloxy-5-nitropyridine was obtained in 95% yield, mp 107–108° (lit.[8] 107.0–107.5°).

2-Isopropyloxy-5-nitropyridine.—Isopropyl iodide (15.3 g, 0.09 mol) was added to the solution of the sodium salt of III (9.2 g, 0.057 mol) in 50 ml of absolute ethanol. The reaction mixture was refluxed until the color of the solution changed to dark brown (about 4 hr). The solvent was removed *in vacuo* and, after steam distillation, the distillate was extracted three times with 30 ml of chloroform. After the chloroform was removed under reduced pressure, the product was recrystallized from ethanol and water, yield 2 g (19%), mp 51.5–52.5°.

Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.40; H, 5.76; N, 15.28.

Registry No.—2-Ethoxy-5-carbethoxypyridine, 24903-80-8; 2-benzyloxy-5-carbethoxypyridine, 24903-81-9; 1-ethyl-5-carbethoxy-2-pyridone, 24903-82-0; 1-isopropyl-5-carbethoxy-2-pyridone, 24903-83-1; 1-benzyl-5-carbethoxy-2-pyridone, 24903-84-2; 2-isopropyloxy-5-nitropyridine, 24903-85-3.

Thietanes. Syntheses, Configurations, and Conformations of 2,4-Diphenylthietanes and Their Oxides

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cis- and *trans*-2,4-diphenylthietane (IV and V), their 1-oxides (VI and VII, respectively), and their 1,1-dioxides (VIII and IX, respectively) have been synthesized. Configurations were assigned primarily from the nmr data. The angles of pucker of *cis*-2,4-diphenylthietane *trans*-1-oxide (VI) and of 3-chlorothietane (X) were calculated from their nmr spectra and were in excellent agreement with the angles of pucker of these compounds determined from X-ray crystal analysis (for VI) and from dipole moment data (for X). Pyrolysis of *cis*- or *trans*-2,4-diphenylthietane 1,1-dioxide (VIII or IX) yielded a mixture of *cis*- and *trans*-1,2-diphenylcyclopropanes.

Because of the unusual stereochemistry observed in the formation and decomposition of the intermediate thiirane 1,1-dioxide in the Ramberg–Bäcklund reaction,[1] some years age we decided to investigate the formation and decomposition, both thermal and catalytic, of substituted thietanes, their monoxides, and dioxides. In this paper, we describe the syntheses and the determinations of configurations and conformations of the 2,4-diphenylthietanes, their monoxides, and dioxides.[2] In subsequent papers we shall report the rearrangement of either *cis*- or *trans*-2,4-diphenylthietane 1,1-dioxide on treatment with ethylmagnesium bromide to *trans*-1,2-diphenylcyclopropanesulfinic acid,[3] the conversion of either *cis*- or *trans*-2,4-diphenylthietane 1-oxide on treatment with potassium *t*-butoxide to *cis*-1,2-diphenylcyclopropanesulfinic acid and *cis*-1,2-diphenylcyclopropanethiol, the rearrangement of 2,4-diphenylthietane 1,1-dioxides with magnesium *t*-butoxide to 3,5-diphenyl-1,2-oxathiolane 2-oxides,[4] and the conversion of *trans*-2,4-diphenylthietane with potassium *t*-butoxide to 2,3,5-triphenylthiophene and 1,2,4,5-tetraphenylbenzene (low yield).

Synthesis.[5]—The thietanes were synthesized by the sequence of reactions depicted in Scheme I. Ethanethiolic acid was added to benzalacetophenone to give 1,3-diphenyl-3-acetylthio-1-propanone (I) in excellent yield (68–99.5%). Compound I was reduced to 1,3-diphenyl-3-hydroxy-1-propanethiol (II) (97.7% yield) with lithium aluminum hydride in tetrahydrofuran, and II was converted without extensive purification to 1,3-diphenyl-3-chloro-1-propanethiol (III) (90.8% yield) with concentrated hydrochloric acid. Compound III was converted to a mixture of *cis*- and *trans*-2,4-diphenylthietanes (IV and V) (mp 40–85°, 95% yield) with aqueous sodium hydroxide. Fractional crystallization of this mixture from ether and/or petroleum ether gave *trans*-2,4-diphenylthietane (V) (12–15% yield) and a sharp-melting complex of approximately equal amounts of the *cis*- and *trans*-2,4-

(1) F. G. Bordwell and E. Doomes, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, No. ORGN 55; F. G. Bordwell, B. B. Jarvis, and P. W. Corfield, *J. Amer. Chem. Soc.*, **90**, 5298 (1968); L. A. Paquette, *Accounts Chem. Res.*, **1**, 209 (1968).

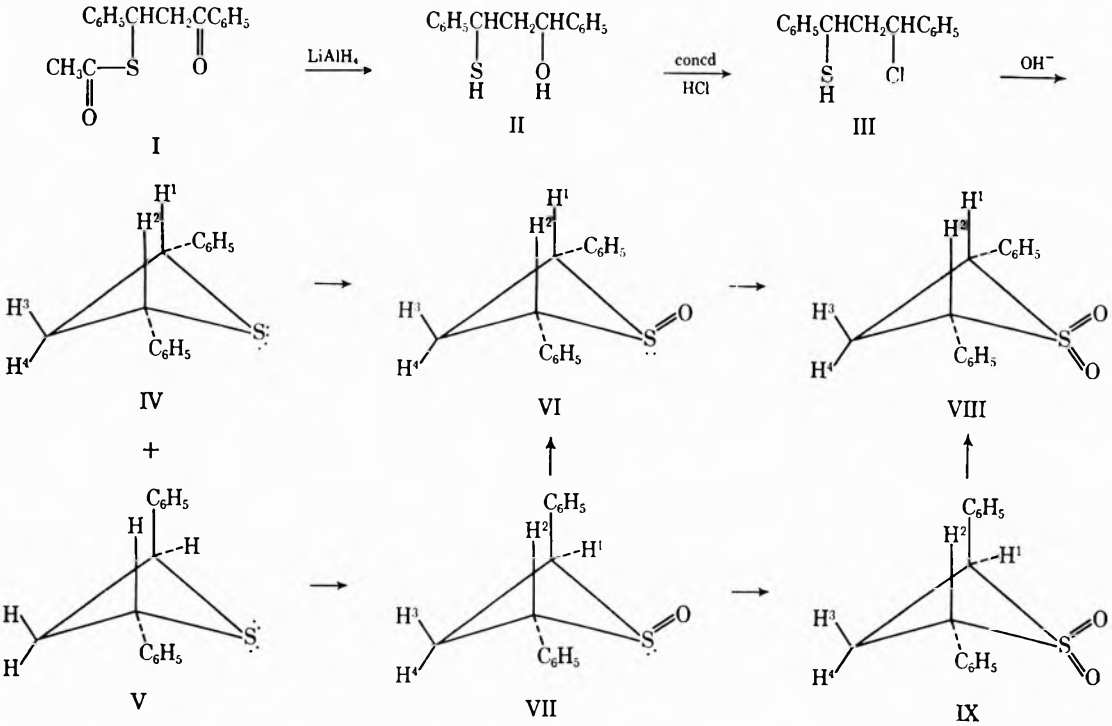
(2) A preliminary account of this work has been published: R. M. Dodson and G. Klose, *Chem. Ind.* (London), 450 (1963).

(3) R. M. Dodson and G. Klose, *ibid.*, 1203 (1963).

(4) R. M. Dodson, P. D. Hammen, and R. A. Davis, *Chem. Commun.*, 9 (1968); correction, *ibid.*, 535 (1968).

(5) (a) The syntheses of thietanes have recently been reviewed: M. Sander, *Chem. Rev.*, **66**, 341 (1966). (b) For more recent methods and references to more recent methods, see L. A. Paquette and M. Rosen, *J. Amer. Chem. Soc.*, **89**, 4102 (1967); *J. Org. Chem.*, **33**, 3027 (1968); L. A. Paquette, M. Rosen, and H. Stucki, *ibid.*, **33**, 3020 (1968); D. C. Dittmer and E. S. Whitman, *ibid.*, **34**, 2004 (1969); A. Ohno, Y. Ohnishi, and G. Tsuchihashi, *Tetrahedron Lett.*, 161, 283 (1969).

Scheme I



diphenylthietanes (IV and V) (mp 61–62°, 57–69% yield).[6] We have not succeeded in isolating pure *cis*-2,4-diphenylthietane (IV). *trans*-2,4-Diphenylthietane (V) was readily oxidized in excellent yields by conventional methods to the corresponding 1-oxide (VII, 89% yield) and 1,1-dioxide (IX, 88% yield). Oxidation of the complex of *cis*- and *trans*-2,4-diphenylthietanes (IV and V) with an equivalent quantity of performic acid yielded a mixture of the 1-oxides which was readily separated by fractional crystallization into *trans*-2,4-diphenylthietane 1-oxide (VII) and *cis*-2,4-diphenylthietane *trans*-1-oxide (VI). We have not succeeded in attempts to prepare *cis*-2,4-diphenylthietane *cis*-1-oxide. Oxidation of compound VI or VII with performic acid yielded the corresponding 1,1-dioxides VIII (94% yield) and IX (94% yield), respectively. Oxidation of the complex of *cis*- and *trans*-2,4-diphenylthietanes (IV and V) with excess performic acid yielded a sharp-melting complex (mp 124–125°) of the corresponding 1,1-dioxides (VIII and IX). This complex could be formed by crystallization of a mixture of equal amounts of *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides (VIII and IX).

Configurations.—Our first evidence on the configurations of the 2,4-diphenylthietanes and their oxides came from studies on equilibration of the 2,4-diphenylthietane monoxides (VI and VII) and dioxides (VIII and IX) in the presence of base. Thus, isomerization of VII or IX with sodium methoxide in methanol gave 96% or more VI or VIII, respectively. This is easily explained by the assumption that the substituted thietane ring is puckered (not flat) and that the phenyl groups in the more stable molecule occupy pseudoequatorial conformations[7] and are, therefore, *cis* to each other. This evidence established the configuration of the phenyl groups in all of the 2,4-diphenylthietanes and their oxides (IV to IX).

Confirmation of these assignments was obtained from a complete analysis of the nmr spectra of compounds IV to IX (Table I). The spectra of *trans*-2,4-diphenylthietane (V) and *trans*-2,4-diphenylthietane 1,1-dioxide (IX) were deceptively simple AA'BB' spectra.[8] Each consisted of two triplets at 500-Hz sweepwidth. Spectra of V taken at 50-Hz sweepwidth were still too simple to permit calculation (13 observable transitions out of a possible 28). The spectrum of V was subtracted from the spectrum of the complex of IV and V. This permitted calculation of the spectrum of IV as an A_2BC system, and thus confirmed the assignment of configuration.

The assignments of the vicinal coupling constants to the *cis* and *trans* protons in IV could not be made directly, since with small rings $^3J_{cis}$ is sometimes larger than $^3J_{trans}$.[9] This problem was readily resolved by consideration of the spectrum of *trans*-2,4-diphenylthietane 1-oxide (VII). Analyzed as an ABCD system, one ^3J had a value of 3.16 Hz. Since in any puckering of the thietane ring of VII the dihedral angle between the pseudoequatorial α proton and the β proton *trans* to it approaches 90°, this small coupling constant was assigned to that interaction, $J_{1,3}$ (VII).[10]

(6) A related sequence of reactions was used by B. M. Trost, W. L. Schinski, and I. B. Mantz [*J. Amer. Chem. Soc.*, **91**, 4321 (1969)] for the synthesis of *cis*- and *trans*-2,4-dimethylthietanes.

(7) This was probably the first reported evidence for a puckered thietane ring (see ref 2). Early thermodynamic and spectroscopic evidence on thietane itself had led to the erroneous conclusion that the ring was planar (C_{2v} symmetry): D. W. Scott, H. L. Finke, W. H. Hubbard, J. P. McCullough C. Katz, M. E. Gross, J. F. Messerly, R. E. Pennington, and G. Waddington, *J. Amer. Chem. Soc.*, **75**, 2795 (1953); ref 5a.

(8) D. M. Grant and H. S. Gutowsky, *J. Chem. Phys.*, **34**, 699 (1961). B. M. Trost, *et al.*,[6] report J_{AB} = 6.9 Hz for *trans*-2,4-dimethylthietane but do not indicate how this value was obtained.

(9) (a) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3218 (1963); H. Weitkamp and F. Korte, *Tetrahedron, Suppl.*, **7**, 75 (1966). (b) Many of our calculations were started before the calculations of W. D. Keller, T. R. Lusebrink, and C. H. Sederholm [*J. Chem. Phys.*, **44**, 782 (1966)] on the nmr spectrum of 3-chlorothietane appeared.

(10) The numbering of the chemical shifts and coupling constants in Table I correspond to the numbering of the protons for IV to IX in Scheme I.

TABLE I[a]

2,4-DIPHENYLTHIETANES

Compd[b]	ν^1	ν^2	ν^3	ν^4	$J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$
					$CDCl_3$[c]					
IV *cis* sulfide	290.6	290.6	199.4	190.0	...[d]	7.35	9.95	7.35	9.95	−11.55
V *trans* sulfide	286	286	199	199	...[e]					
VI *cis* oxide	257.3	257.3	180.7	141.7	...[d]	9.53	12.62	9.53	12.62	−12.85
VII *trans* oxide	285.1	269.7	193.5	168.6	−1.12	3.16	8.79	10.24	11.90	−13.81
VIII *cis* dioxide	321.5	321.5	169.9	157.9	...[d]	9.17	11.12	9.17	11.12	−11.91
IX *trans* dioxide	335.0	335.0	170.5	170.5	...[e]					
					30% $CDCl_3$ in C_6H_6[f]					
VI *cis* oxide	248	248	150	122	...[d]	9.5	13	9.5	13	−13
VII *trans* oxide	264	253	162	138	~1	3.0	8.5	10.0	12	−13.5

[a] Recorded in hertz downfield from tetramethylsilane; determined at 60 MHz. [b] *cis* and *trans* refer to the relationship of the phenyl groups. [c] These spectra were analyzed by use of the LAOCOON-2 or LAOCOON-3 program of A. A. Bothner-By and S. M. Castellano. The chemical shifts vary slightly with concentration but have not been extrapolated to zero concentration. The coupling constants are reported to three significance figures, since these are the values used to calculate conformations (see below). None of the calculated probable errors of the parameter sets exceeded 0.058 Hz. [d] Coupling constants between A_2 protons in an A_2BC system cannot be directly observed. [e] The simplicity of the spectra made these coupling constants unobservable. $J_{1,3} + J_{1,4} = ca.$ 15 Hz for *trans*-2,4-diphenylthietane (V) and *ca.* 17.5 Hz for *trans*-2,4-diphenylthietane dioxide (IX). [f] A mixture of 30% deuteriochloroform in benzene instead of pure benzene was used to increase solubilities. These spectra were not fitted by computer but were analyzed directly by analogy to the spectra in $CDCl_3$. Accuracy does not exceed ±0.5 Hz.

This immediately led to assignments of the other three protons in the molecule and to the conclusion that $^3J_{trans} > {}^3J_{cis}$ for the pseudoaxial proton. The relative signs of the coupling constants for the protons in VII were determined by the double irradiation technique of Freeman and Anderson.[11] From the assignments of chemical shifts and coupling constants for VII, the assignments of chemical shifts and coupling constants for IV, VI, and VIII immediately follow, and the configurations of the phenyl groups are confirmed.

The configuration of the oxygen on sulfur in *cis*-2,4-diphenylthietane *trans*-1-oxide (VI) was assigned on the following bases. (1) Peracids selectively oxidize the sterically less hindered pair of electrons on sulfur in cyclic compounds and yield predominantly equatorial sulfoxides.[12] (2) Compound VII ran faster on thin layer chromatography than VI.[12] (3) The S=O bond shields groups which lie directly behind it (along the axis).[12b,c,13] Thus, on oxidation of the thietane IV to the 1-oxide VI, H^4, which lies almost directly behind the S=O bond in a puckered *cis*-2,4-diphenylthietane *trans*-1-oxide, was shielded to a much greater extent than H^3 (see Table II).[14] (4) A hydrogen atom (H^1 and H^2) in the conformational relationship to a vicinal sulfoxide group depicted in VI should be markedly shielded by the S=O bond and/or the unshared pair of electrons (see Table II).[15] This assignment of the configuration of *cis*-2,4-diphenylthietane *trans*-1-oxide (VI) has been confirmed very recently by a crystal analysis of this compound.[16]

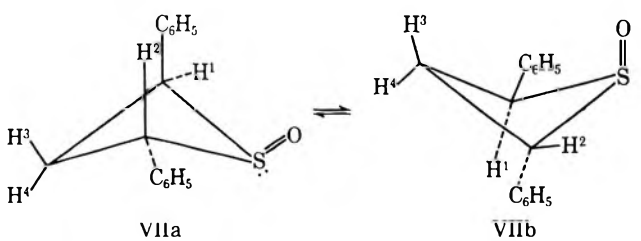
TABLE II

$\Delta\nu$ (SULFOXIDE − SULFIDE)

	$\Delta\nu$, Hz			
	H^1	H^2	H^3	H^4
(VI − IV) *cis*	−33.3	−33.3	−18.7	−48.3
(VII − V) *trans*	−0.9	−16.3	−5.5	−30.4

Conformations.—The *cis*-2,4-diphenylthietanes (IV, VI, VIII) should exist almost exclusively in the conformations depicted in Scheme I. The equilibrium studies on VI and VIII support this conclusion.

The *trans*-2,4-diphenylthietane 1-oxide (VII) can exist as a mixture of the conformers VIIa and VIIb. That VII exists largely as one conformer can be seen immediately from the analysis of its nmr spectrum. If VIIa and VIIb were of comparable importance, $J_{1,3}$ should be approximately equal to $J_{2,4}$. However $J_{1,3}$ (3.16) is the smallest vicinal coupling constant, while $J_{2,4}$ (11.90) is the largest vicinal coupling constant. The preferred conformation of *trans*-2,4-diphenylthietane 1-oxide (VII) followed from the data presented in Table II. Thus on oxidation of the sulfide to the sulfoxide, H^4 was shielded to a greater extent than H^3, and H^2 was shielded to a greater extent than H^1. In the preferred conformation, therefore, the oxygen on sulfur was pseudoequatorial (VIIa). Further evidence for this was obtained from the changes of the chemical shifts of H^1 and H^2 with change of solvent;[12c,15,17] $\Delta\nu$ (C_6H_6–$CDCl_3$) for H^1 = −21.1



VIIa VIIb

(11) R. Freemen and W. A. Anderson, *J. Chem. Phys.*, **37**, 2053 (1962).

(12) (a) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965); (b) R. Nagarajan, B. H. Chollar, and R. M. Dodson, *Chem. Commun.*, 550 (1967); (c) P. B. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 552 (1967).

(13) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *ibid.*, 759 (1966); C. R. Johnson and W. O. Siegl, *Tetrahedron Lett.*, 1879 (1969).

(14) An analysis of the shielding contributions from the ring currents of the 2- and 4-phenyl groups in various conformations indicated high improbability that the relative shielding of H^3 and H^4 resulted from this source: C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(15) R. A. Archer and P. V. DeMarco, *J. Amer. Chem. Soc.*, **91**, 1530 (1969); D. H. R. Barton, F. Comer, and P. G. Sammes, *ibid.*, **91**, 1529 (1969); R. M. Dodson and R. F. Sauers, unpublished work on the stereochemistry of substituted 2,5-dihydrothiophene 1-oxides.

(16) Private communication: G. L. Hardgrove, J. S. Bratholdt, and M. M. Lien, Department of Chemistry, St. Olaf College, Northfield, Minn.

(17) E. T. Strom, B. S. Snowden, Jr., and P. A. Toldan, *Chem. Commun.*, 50 (1969); M. Nishio, *ibid.*, 51 (1969); P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969); R. D. G. Copper, P. V. DeMarco, and D. O. Spry, *ibid.*, **91**, 1528 (1969).

and for $H^2 = -16.7$ Hz. Although the difference between these values is small "the values are consistent with the conclusion that H^2 is *cis* and H^1 is *trans* to the oxygen attached to sulfur."

An estimate of the position of the equilibrium VIIa ⇄ VIIb can be obtained as follows. Since a 1,3-diaxial phenyl–hydrogen interaction occurs in VII but not in VI, the angle of pucker of *cis*-2,4-diphenylthietane *trans*-1-oxide (VI) should be at least as large as the angle of pucker of VIIa or VIIb. If it is assumed that the angle of pucker of VIIa and VIIb are equal and are also equal to the angle of pucker of VI then $J_{1,4}$(VI) ≅ $J_{2,4}$(VIIa) ≅ $J_{1,3}$(VIIb) ≅ 12.6 Hz. From these assumptions and from $J_{1,3}$ and $J_{2,3}$ for VII, one can calculate that VII consists of *ca.* 93% VIIa and 7% VIIb and that $J_{1,3}$(VIIa) = 2.44. Any decrease in the angle of pucker of VIIa and VIIb compared with VI would lead to calculations showing an increased quantity of VIIa. Any moderate decrease of the angle of pucker of VIIbc ompared with VIIa will have little effect on the calculations. The above conclusions are consistent with the recent observations of Johnson and Siegel.[18] They found that the "sulfinyl oxygen in a four-membered ring exerts a pseudoequatorial preference," and that equilibration of *cis*- and *trans*-3-*p*-chlorophenylthietane 1-oxide gives largely the *cis* isomer (*cis*/*trans* ratio of *ca.* 87:13).

Calculation of Dihedral Angles.—The dihedral angles HCCH of *cis*- and *trans*-2,4-diphenylthietane 1-oxides (VI and VII) were calculated from their nmr spectra in the following way. (1) The vicinal coupling constants were fitted to an equation of the form $^3J_{H,H'} = A \cos^2 \phi + B \cos \phi + C$.[19] (2) The geminal angle H^3CH^4 of all of the thietanes was assigned the same value, 112°, the geminal angle HCH found in trimethylene oxide.[20] The internal angle $C^2C^3C^4$ of all of the thietanes was also assigned the same value, 94°, the value published by Allenmark[21] for this same angle in *trans*-3-carboxythietane 1-oxide. The use of these angles gave a value of $\omega = 127.49°$, for the projection of the geminal angle H^3CH^4 perpendicular to the C^2–C^3 bond. (3) The coupling constants determined for *trans*-2,4-diphenylthietane 1-oxide (VII) were assigned entirely to the principle conformer (VIIa) Since we have estimated that 7% of VII could exist as the conformer VIIb, a comparable error in these calculations may result.

By use of the above and the coupling constants from the nmr spectra of VII and VI, the following six nonlinear equations in six unknowns were written.

trans-Oxide (VII)

$$J_{1,4} = 8.79 = A \cos^2 \Phi + B \cos \Phi + C$$
$$J_{1,3} = 3.16 = A \cos^2 (\omega - \Phi) + B \cos (\omega - \Phi) + C$$
$$J_{2,3} = 10.24 = A \cos^2 \Phi' + B \cos \Phi' + C$$
$$J_{2,4} = 11.90 = A \cos^2 (\omega + \Phi') + B \cos (\omega + \Phi') + C$$

cis-Oxide (VI)

$$J_{1,3} = 9.53 = A \cos^2 \Phi'' + B \cos \Phi'' + C$$
$$J_{1,4} = 12.62 = A \cos^2 (\omega + \Phi'') + B \cos (\omega + \Phi'') + C$$

Solution of these equations, gave the equation

$$^3J_{H,H'} = 9.9 \cos^2 \phi - 0.9 \cos \phi + 3.12 \quad (1)$$

and the following dihedral angles[22] (degrees)

	∠H^1CCH^3	∠H^1CCH^4	∠H^2CCH^3	∠H^2CCH^4
VII *trans*-oxide	91.0	36.5	26.5	154.0
VI *cis*-oxide	31.6	159.1		

From the above it is immediately apparent that the *trans*-2,4-diphenylthietane 1-oxide (VII) is a badly distorted molecule. The C^2 atom is rotated to a greater degree (37°) than the C^4 atom (27°). This can be readily understood if the C_6H_5 group on C^2 is *cis* to the oxygen on sulfur. Thus, these calculations also confirm the conformation (S=O pseudoequatorial) previously assigned to VII.

Calculation of Angles of Pucker.—To calculate the shape of the thietane molecule, it is necessary to have two adjacent angles and the lengths of the sides. The bond lengths used in this calculation were those used by Gwinn[23] and coworkers [S–C = 1.833 Å; C–C = 1.54 Å] in their detailed analysis of the microwave spectrum of thietane. These bond lengths are in excellent agreement with those listed by Sutton.[24] From the dihedral angle H^1CCH^3 of *cis*-2,4-diphenylthietane *trans*-1-oxide (VI), the angles given in (2) of the preceding section, an assignment of 112° to the geminal angle H^1C^2–C_5H_5, and the bond lengths given above, the dihedral angle between the C^2–S–C^4 and the C^2–C^3–C^4 planes of VI can be calculated to be 140.3° (angle of pucker 39.7°).[25] A crystal structure analysis[16] still in progress gave a value of 138.8° (angle of pucker 41.2°) for the angle between these planes.[25a] The angle of pucker of thietane itself, determined from its microwave spectrum,[23] is 32°. We calculated an angle of pucker of 29.7° for *trans*-3-carboxythietane 1-oxide from the unrefined data given by Allenmark.[21]

Unfortunately, sufficient data were not available to fit completely the Barfield–Karplus[19] equation to *cis*-2,4-diphenylthietane (IV) and *cis*-2,4-diphenylthietane dioxide (VIII). However, if it is assumed that that portion of eq 1 determining the angular dependence of the coupling constants remains unchanged and that changes in oxidation state (inductive effects) largely affect the value of the constant C, two simultaneous equations in two unknowns can be written and solved for the dihedral angle H^1CCH^3 and C. For *cis*-2,4-diphenylthietane dioxide (VIII) this procedure gave $C = 2.2$ and ϕ (∠H^1CCH^3) = 27.7°. This corresponds to a dihedral angles between the C^2–S–C^4 and the

(18) C. R. Johnson and W. O. Siegl, *J. Amer. Chem. Soc.*, **91**, 2796 (1969).

(19) (a) M. Barfield and M. Karplus, *ibid.*, **91**, 1 (1969); (b) M. Barfield and D. M. Grant, *Advan. Magn. Resonance*, **1**, 187 (1965).

(20) J. Fernandez, R. J. Myers, and W. D. Gwinn, *J. Chem. Phys.*, **23**, 758 (1955). It should be realized that the potential energy function for the ring-puckering vibration of trimethylene oxide also has a double minimum: S. I. Chan, T. R. Borgers, J. W. Russell, H. L. Strauss, and W. D. Gwinn, *ibid.*, **44**, 1103 (1966).

(21) S. Allenmark, *Ark. Kemi*, **26**, 73 (1967).

(22) A similar calculation using the value $J_{1,3}$(VIIa) = 2.44, calculated above for the principle conformer of VII, gave a slightly different equation

$$^3J_{H,H'} = 10.75 \cos^2 \phi - 0.9 \cos \phi + 2.43$$

but gave dihedral angles practically identical with those calculated above (maximum difference ±0.8°).

(23) D. O. Harris, H. W. Harrington, A. C. Luntz, and W. D. Gwinn, *J. Chem. Phys.*, **44**, 3467 (1966); private communication from Dr. D. O. Harris.

(24) "Tables of Interatomic Distances and Configurations in Molecules and Ions," L. E. Sutton, Ed., Special Publications No. 11 and No. 18, The Chemical Society, London, 1958 and 1965.

(25) Allowance was made for the projection of the geminal angles $H^3C^3H^4$ and H^1C^2–C_6H_5 (both assigned values of 112°) perpendicular to the C^2–C^3 bond. Since the projected angle of H^1C^2–C_6H_5 will change with change of the angle S–C^2–C^3, an iterative calculation was used.

(25a) Note Added in Proof.—Refinement of calculations gave a value of 41.9° for this angle.[16]

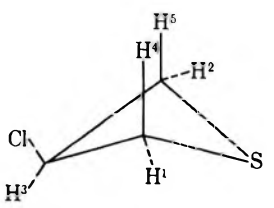
C^2–C^3–C^4 planes of 145° and an angle of pucker of 35°.

Application of this same procedure to the nmr data for *cis*-2,4-diphenylthietane (IV) gave the equation[26]

$$^3J = 9.9 \cos^2 \phi - 0.9 \cos \phi + 0.7 \quad (2)$$

and a calculated dihedral $\phi(H^1CCH^3) = 30.0°$. This gave a dihedral angle (angle between the planes C^2–S–C^4 and C^2–C^3–C^4) of 142.3° (angle of pucker 37.7°) for IV.

The reliability of this eq 2, when applied to thietanes, can be checked in two ways. Keller and coworkers[9b] have analyzed in detail the nmr spectrum of 3-chlorothietane (X). If it is assumed that X exists largely in the conformation depicted [this same assumption was made by Arbuzov (see ref 27 below)] then from $J_{1,3}$ and $J_{3,4}$ and the above equation one can calculate the dihedral angles $H^1CCH^3 = 27.6°$ and $H^4CCH^3 =$



X

$J_{1,3} = 7.670$ Hz

$J_{3,4} = 9.343$ Hz

152.9°. By the method used above, the dihedral angle between the C^2–S–C^4 and C^2–C^3–C^4 planes can be calculated to be 142.4° (angle of pucker 37.6°). This is in excellent agreement with the dihedral angle of 143° calculated for 3-chlorothietane by Arbuzov and coworkers[27] from dipole moment data. Finally, from the calculated dihedral angles, $\angle H^1CCH^3 = 27.6°$ and $\angle H^4CCH^3 = 152.9°$, the projection of the geminal angle $H^4C^2H^1$ perpendicular to the C^2–C^3 bond is equal to 125.3°. From the usual assignment of a value of 112° to the geminal angle $H^4C^2H^1$ and from the calculated angle of pucker, the projected geminal angle $\omega = 129.5°$ is determined, in fair agreement with value of 125.3° found above.

Pyrolysis[2,28] of either *cis*- or *trans*-2,4-diphenylthietane 1,1-dioxide (VIII or IX) at 250° led to the evolution of sulfur dioxide and yielded a mixture of *cis*- and *trans*-1,2-diphenylcyclopropanes that approximated in composition the equilibrium mixture expected at that temperature.[29]

Experimental Section[30]

1,3-Diphenyl-3-acetylthio-1-propanone (I).—Benzalacetophenone (317.6 g, 1.525 mol) was dissolved in a mixture of benzene (300 ml) and petroleum ether (600 ml). The resulting soluton was heated to reflux. While it was stirred, ethanethiolic acid (200 g, 2.633 mol) was added from a dropping funnel over a 1-hr period. Stirring and heating were continued for 1 hr more. When the reaction was cooled, 1,3-diphenyl-3-acetylthio-1-propanone (431.5 g, 1.517 mol, 99.5%, mp 76.5–77.5°, ν_{max}^{Nujol} 1675 cm^{-1}) separated as a pale yellow crystalline solid. Crystallization from petroleum ether removed the color and raised the melting point to 77–78°. In one instance mp 85–86° was obtained by crystallization from methanol.

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67. Found: C, 71.62; H, 5.83.

1,3-Diphenyl-3-hydroxy-1-propanethiol (II).—1,3-Diphenyl-3-acetylthio-1-propanone (I) (100.00 g, 0.352 mol) was dissolved in purified, anhydrous tetrahydrofuran (300 ml) and added with stirring over 1 hr to lithium aluminum hydride (30 g, 0.786 mol) suspended in tetrahydrofuran (400 ml). After the addition was complete, the reaction mixture was heated under reflux for 2 hr and was then cooled to room temperature. The excess lithium aluminum hydride was decomposed by the slow addition of ethyl acetate, followed by the addition of a few milliliters of water. The reaction mixture was poured onto concentrated hydrochloric acid (800 ml) and ice, and the product was extracted with several portions of ether. The ether solution was washed thoroughly with water. To further purify II, it was extracted from the ether with several portions of 10% aqueous sodium hydroxide. The product was immediately liberated from the basic solution with concentrated hydrochloric acid and was extracted with ether. The ether solution was washed thoroughly with water, dried (magnesium sulfate), and evaporated. The 1,3-diphenyl-3-hydroxy-1-propanethiol [84.04 g, 0.344 mol, 97.7%; ν_{max}^{neat} 3350 (s), (OH), 2992 (w), 2940 (w), 2840 (w), 2520 cm^{-1} (w), (SH)] was obtained as a viscous, golden-yellow oil, which did not solidify upon being cooled and which was used directly in the next step.

1,3-Diphenyl-3-chloro-1-propanethiol (III).—1,3-Diphenyl-3-hydroxy-1-propanethiol (84.04 g, 0.344 mol) was dissolved in ether (400 ml) and added during 1 hr at room temperature with stirring to concentrated hydrochloric acid. After being stirred vigorously for an additional hour, the reaction was quenched with water (2 l.), separated, and extracted with several portions of ether. The ether extracts were washed with water, dried over magnesium sulfate, and then evaporated. The 1,3-diphenyl-3-chloropropanethiol [82.0 g, 0.313 mol, 90.8%; ν_{max}^{neat} 2992 (w), 2910 (w), 2520 cm^{-1} (w) (SH)] was obtained as a dark yellow oil which did not solidify upon being cooled and which was used directly in the next step.

***cis*- and *trans*-2,4-Diphenylthietanes.**—1,3-Diphenyl-3-chloropropanethiol (III) (82.0 g, 0.313 mol) was dissolved in ether (300 ml) and was added slowly with stirring over a 1-hr period to cold (ice bath) 10% aqueous sodium hydroxide (800 ml). Stirring was continued for an additional 2 hr in the cold. The ether layer was separated and the sodium hydroxide solution was extracted with several portions of ether. The combined extracts were washed thoroughly with water, dried over magnesium sulfate, and then reduced to a low volume. When the solution was cooled, *trans*-2,4-diphenylthietane (V) (10.60 g, 0.0469 mol, 15%), mp 96–97°, separated first in the form of long needles. Crystallization from petroleum ether, gave *trans*-2,4-diphenylthietane: mp 102–103°; $\lambda_{max}^{ethanol}$ 217 nm (ϵ 21,470); ν_{max}^{Nujol} 699 (s), 730 (m), 763 (s), 1081 (m), 1490 (m), 1600 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{14}S$ (226.34): C, 79.60; H, 6.23. Found: C, 79.49; H, 6.20; mol wt (Rast) 233.

The ether mother liquors from the above isolation were evaporated. White crystals (51.2 g, 0.227 mol, 72%), mp 50–60°, were obtained. Further crystallization of this material from petroleum ether gave a sharp-melting complex of approximately equal quantities of *cis*- and *trans*-2,4-diphenylthietane, mp 61–62° (40.11 g, 0.1774 mol, 56.7%).

Anal. Calcd for $C_{15}H_{14}S$ (226.34): C, 79.60; H, 6.23. Found: C, 79.41; H, 6.34; mol wt (Rast) 233.

***trans*-2,4-Diphenylthietane 1-Oxide (VII).**—To *trans*-2,4-diphenylthietane (1.00 g, 0.0044 mol, mp 96–97°) dissolved in methanol (35 ml) and 96% formic acid (3 ml) was added 30% hydrogen peroxide (0.50 g, 0.0044 mol). The mixture was

(26) Use of the equation given in footnote 22, yielded $\phi = 29.6°$ and $C = 0.0$. It is known that C approximates zero for compounds free of strongly electronegative substituents (see ref 19b).

(27) B. A. Arbuzov, O. N. Nuretdinova, and A. N. Vereschagin, *Dokl. Akad. Nauk SSSR*, **172** (3), 591 (1967); *Chem. Abstr.*, **66**, 89337y (1967).

(28) For recent examples of the pyrolysis of cyclic sulfones, see E. J. Moriconi, R. E. Misner, and T. E. Brady, *J. Org. Chem.*, **34**, 1651 (1969), and many references contained therein.

(29) L. B. Rodewald and C. H. de Puy, *Tetrahedron Lett.*, 2951 (1964); R. J. Crawford and T. R. Lynch, *Can. J. Chem.*, **46**, 1457 (1968).

(30) Melting points were taken on a Fisher-Johns melting point apparatus, calibrated against a set of standard compounds. Petroleum ether refers to that fraction of bp 60–68°. The nmr spectra were determined on a Varian A-60 spectrometer in solutions of approximately 20%. Spectra on compounds VI, VII, and VIII and the complex (IV and V) were determined at 50-Hz sweepwidth and calibrated using a Hewlett–Packard Model 202A low-frequency function generator. The nmr data on compounds VI, VII, and VIII are the average of at least four spectra.

warmed on the steam bath just below reflux temperature for 12 hr. Partial evaporation of the solvent and cooling led to precipitation of *trans*-2,4-diphenylthietane 1-oxide (0.70 g, mp 152–153°). Further condensation and cooling of the mother liquors yielded a second crop (0.25 g, mp 152–153°; total yield 0.95 g, 88.8%). Recrystallization from methanol–water yielded pure *trans*-2,4-diphenylthietane 1-oxide (VII), mp 154–155°, ν_{max}^{Nujol} 1064 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}OS$: C, 74.34; H, 5.82. Found: C, 74.21; H, 5.88.

***cis*-2,4-Diphenylthietane *trans*-1-Oxide (VI).**—Oxidation of the molecular complex of *cis*- and *trans*-2,4-diphenylthietanes (16.0 g, 0.070 mol, mp 59–61°) by the method described above yielded a mixture of *cis*- and *trans*-2,4-diphenylthietane 1-oxides (15.7 g, 0.065 mol, 93%), mp 100–120°. Fractional crystallization of this material from benzene yielded *trans*-2,4-diphenylthietane 1-oxide (2.13 g, 0.0089 mol, 14%), mp 153–154°, and *cis*-2,4-diphenylthietane *trans*-1-oxide (8.78 g, 0.0362 mol, 55.7%), mp 127–129°. Thin layer chromatography showed that the *cis* isomer still contained a small amount of the *trans* isomer. Two crystallizations from benzene yielded pure *cis*-2,4-diphenylthietane *trans*-1-oxide, mp 135.5–136.5°.

In an alternate preparation, the molecular complex of *cis*- and *trans*-2,4-diphenylthietanes (10.0 g) was oxidized by the method described above, and the *trans*-2,4-diphenylthietane 1-oxide (1.20 g, 11% yield, mp 152–155°) was isolated by crystallization from petroleum ether–chloroform. The material remaining in the mother liquors was then isomerized with sodium methoxide in methanol (see below). Crystallization of the product from petroleum ether–chloroform yielded pure *cis*-2,4-diphenylthietane *trans*-1-oxide (3.86 g, 0.016 mol, 36%), mp 135–137°, ν_{max}^{Nujol} 1069 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}OS$: C, 74.34; H, 5.82. Found: C, 74.20; H, 6.11.

Isomerization of *trans*-2,4-Diphenylthietane 1-Oxide.—A solution of pure *trans*-2,4-diphenylthietane 1-oxide (VII) (0.70 g, mp 153–154°) in methanol (125 ml) containing sodium methoxide (2.8 g) was heated under reflux for 48 hr. The volume of the solution was reduced to 20 ml by distillation, water was added, and the solution was cooled. Light yellow crystals (0.641 g, 0.00265 mol, 91.6%), mp 123–127°, separated. Thin layer chromatography [silica gel G, ethyl acetate–benzene (1:4); product was detected with 2% aqueous potassium permanganate solution] showed the presence of two products, a very small quantity of the faster running product corresponding in position to *trans*-2,4-diphenylthietane 1-oxide and a much larger quantity of a slower running product corresponding in position to *cis*-2,4-diphenylthietane *trans*-1-oxide.

An nmr analysis on a similarly prepared mixture indicated the presence of approximately 96% *cis*- and 4% *trans*-2,4-diphenylthietane 1-oxides. Isomerization of *cis*-2,4-diphenylthietane *trans*-1-oxide under similar conditions gave similar results.

***trans*-2,4-Diphenylthietane 1,1-Dioxide (IX).** A.—To a solution of *trans*-2,4-diphenylthietane (6.00 g, 0.0264 mol, mp 96–97°) in carbon tetrachloride (75 ml) and 96% formic acid (60 ml) was added slowly, with stirring, hydrogen peroxide (30%, 60 ml) over a 0.5-hr period. During this addition the temperature rose to about 50°. Stirring at this temperature was continued for 4 hr. The reaction mixture was poured into brine, the carbon tetrachloride layer was separated, and the aqueous layer was extracted with seveal portions of carbon tetrachloride. The combined extracts were washed with water and dried over sodium sulfate. After distillation to a volume of approximately 100 ml, *trans*-2,4-diphenylthietane 1,1-dioxide (5.50 g, 0.0213 mol, 80.3%), mp 166–167°, was obtained in the form of fine white crystals. An additional 0.60 g of IX, mp 164–166°, was obtained from the mother liquors, total yield 89.1%. An analytical sample showed the following properties: mp 166–167°; $\lambda_{max}^{ethanol}$ 226.0 nm (ϵ 28,533); ν_{max}^{Nujol} 1117 (s), 1159 (s), 1183 (s), 1193 (m), 1312 (s), cm^{-1} (–SO_2–).

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.47; H, 5.71.

B.—Oxidation of *trans*-2,4-diphenylthietane 1-oxide (VII) (0.20 g, mp 152–153°) by the above method yielded *trans*-2,4-diphenylthietane 1,1-dioxide (0.20 g, 93.9%), mp 165–167°, identical in all respects (mixture melting point, ir spectrum) with that prepared above.

***cis*-2,4-Diphenylthietane 1,1-Dioxide (VIII).**—Oxidation of *cis*-2,4-diphenylthietane *trans*-1-oxide (VI) (0.20 g, mp 135–136°) by the method described above (20 hr) yielded *cis*-2,4-diphenylthietane 1,1-dioxide (0.20 g, 93.9%), mp 162.5–163.5°, identical with that from the isomerization of the *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxide complex (below).

Complex of *cis*- and *trans*-2,4-Diphenylthietane 1,1-Dioxides.—Oxidation of the sharp-melting complex of *cis*- and *trans*-2,4-diphenylthietanes (25.0 g, mp 59–60°) by the method described above yielded 25.5 g (92.1%) of the complex of *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides, mp 121–124°. Crystallization from acetone–petroleum ether raised the melting point to 124–125°.

This same complex was obtained by mixing equal amounts of *cis*-2,4-diphenylthietane 1,1-dioxide (0.50 g, mp 165–166°) and *trans*-2,4-diphenylthietane 1,1-dioxide (0.50 g, mp 166–167°) (mixture had mp 125–150°) and crystallizing the mixture from methanol–water (complex, mp and mmp 124–125°).

***cis*-2,4-Diphenylthietane 1,1-Dioxide (VIII) from Isomerization of the Above Complex.**—A solution of the 2,4-diphenylthietane 1,1-dioxide complex (10.00 g, 0.039 mol, mp 123–124°) and sodium methoxide (20.00 g, 0.11 mol) in methanol (300 ml) was heated under reflux for 45 hr. Isolation of the product followed by its crystallization from petroleum ether yielded *cis*-2,4-diphenylthietane 1,1-dioxide (VIII) (8.70 g, 87%): mp 165–166°; $\lambda_{max}^{ethanol}$ 225.2 nm (ϵ 27,050); ν_{max}^{Nujol} 1139, 1178, 1309 cm^{-1} (–SO_2–).

Anal. Calcd for $C_{15}H_{14}O_2S$(258.3): C, 69.74; H, 5.46. Found: C, 69.56; H, 5.49; mol wt (Rast) 253.2.

Isomerization of *trans*-2,4-diphenylthietane 1,1-dioxide (IX) using the above method gave similar results. A nmr analysis of the product of isomerization (97% yield) of the *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxide complex indicated that it consisted of at least 96% *cis* isomer.

Pyrolysis of *cis*-2,4-Diphenylthietane 1,1-Dioxide.—*cis*-2,4-Diphenylthietane 1,1-dioxide (1.00 g, 0.0039 mol, mp 165–166°) was pyrolyzed in a small distilling flask heated in a metal bath. With a bath temperature of 250°, sulfur dioxide was vigorously evolved. Heating at 250° was continued for 15 min. 1,2-Diphenylcyclopropane (0.70 g, 0.0037 mol, 93%, $n^{26}D$ 1.5952) was distilled (70 min) as a light yellow liquid.

The mixtures of *cis*- and *trans*-1,2-diphenylcyclopropanes were analyzed by gas chromatography using a column (0.25 in. × 10 ft) of Dow silicone high-vacuum grease (20%) absorbed on Johns–Manville Chromosorb W (60-80 mesh) at temperatures of 180 and 220°. The ratios of *cis*/*trans*-diphenylcyclopropanes from *cis*-2,4-diphenylthietane dioxide (VII) and *trans*-2,4-diphenylthietane dioxide (VIII) were 0.131 and 0.134, respectively. To determine whether extensive isomerization was occurring during analysis, a sample of 1,2-diphenylcyclopropane consisting largely of the *cis* isomer was analyzed at both 180 and 220° with comparable results (*cis*/*trans* = 3.7 (180°); 3.8 (220°).

For identification, pure samples of *cis*- and *trans*-1,2-diphenylcyclopropanes were prepared by vapor phase chromatography. *cis*-1,2-Diphenylcyclopropane: mp 37.5–38°, $n^{26}D$ 1.5870; lit.[31] mp 36.7°, 38–38.5°, $n^{20}D$ 1.5892. *trans*-1,2-Diphenylcyclopropane: $n^{26}D$ 1.5965; lit.[31] $n^{20}D$ 1.5995.

Anal. Calcd for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.66; H, 7.56.

The nmr spectra of the pure samples of the *cis*- and *trans*-1,2-diphenylcyclopropanes, while not analyzed in detail, were consistent with the assigned structures.

Registry No.—I, 24621-54-3; II, 24621-55-4; III, 24621-56-5; IV, 24609-87-8; V, 24609-88-9; VI, 24605-73-0; VIIa, 24609-89-0; VIII, 18744-27-9; IX, 24609-91-4.

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(31) D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer, *J. Amer. Chem. Soc.*, **83**, 4838 (1961); B. A. Kazanskii, M. Yu Lukina, I. L. Safanova, V. T. Aleksanyan, and Kh. E. Sterin *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1280 (1958); *Chem. Abstr.*, **53**, 4158 (1959).

Synthesis of 5-Substituted 1-(1-Adamantyl)tetrazoles and Related Compounds

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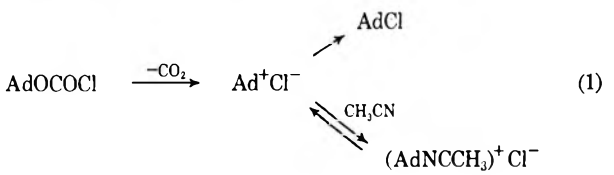
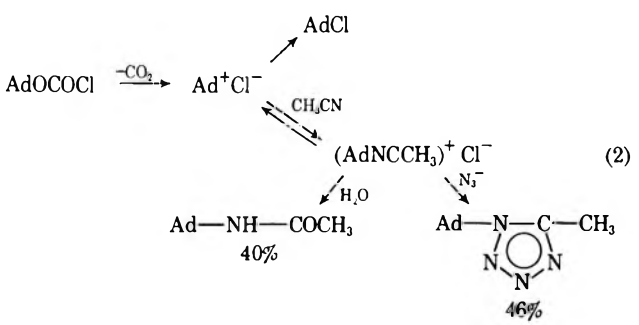
The preparation of 5-substituted 1-(1-adamantyl)tetrazoles has been carried out under neutral conditions, at ambient temperatures, by the reaction of 1-adamantyl iodide with silver hexafluoroantimonate in the appropriate nitrile, followed by addition of a solution of tetraethylammonium azide; the substituents which have been incorporated are methyl, ethyl, propyl, isopropyl, phenyl, vinyl, α-methylvinyl, and *trans*-β-phenylvinyl. By addition of water, rather than azide ion, N-(1-adamantyl)acrylamide and its α-methyl and *trans*-β-phenyl derivatives were prepared. 1-Adamantyl azidoformate and 1-adamantyl azide have also been prepared and characterized.

During a recent investigation of the decomposition of 1-adamantyl chloroformate in a variety of solvents,[1] it was found that the decomposition in dry acetonitrile was accompanied by a competing solvolysis (eq 1). In



(1)

fairly concentrated solution, a precipitate was formed and, upon addition of water, a mixture of 1-adamantyl chloride and N-(1-adamantyl)acetamide was obtained (eq 2). It has been found that precipitation does not



(2)

occur in more dilute solution and titration of the acid developed at 25.0°, after hydrolysis of aliquots of solution, shows that the concentration of the acetonitrilium chloride[2] reaches a maximum after about 8 min and then, over a period of about 4 hr, irreversible conversion to 1-adamantyl chloride takes place.

Trapping the acetonitrilium chloride with azide ion leads to 1-(1-adamantyl)-5-methyltetrazole and, by use of other nitriles as the solvent, the method can be adapted to yield 5-substituted 1-(1-adamantyl)tetrazoles in general. The technique was used to give 1-(1-adamantyl)-5-methyltetrazole in 46% yield by addition of 1-adamantyl chloroformate to sodium azide in acetonitrile. Neither 1-adamantyl azide nor 1-adamantyl azidoformate was observed as products of this reaction. The tetrazole yield is similar to the 40% N-(1-adamantyl)acetamide formed when hydrolysis follows upon solvolysis–decomposition.[1]

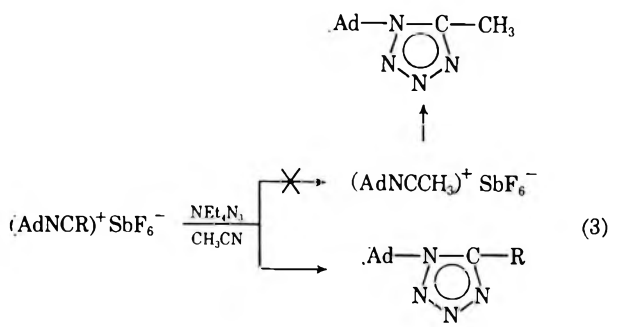
Yields by this technique are limited by the concurrent irreversible decomposition to 1-adamantyl chloride. This competition can be circumvented by use of silver hexafluoroantimonate which removes the nucleophilic chloride ions from solution and replaces them by non-nucleophilic hexafluoroantimonate ions.

$$\text{AdOCOCl} + \text{AgSbF}_6 \xrightarrow{\text{RCN}} (\text{AdNCR})^+\text{SbF}_6^- + \text{CO}_2 + \text{AgCl}\downarrow$$

1-Adamantyl iodide reacts extremely rapidly with silver hexafluoroantimonate and this precursor can be prepared in better than 90% yields by a modification of the one-step reaction of 1-adamantanol with hydriodic acid which was reported by Schleyer and Nicholas.[3] Accordingly, we substituted, as our means of generating the intermediate nitrilium salt, the following reaction.

$$\text{AdI} + \text{AgSbF}_6 \xrightarrow{\text{RCN}} (\text{AdNCR})^+\text{SbF}_6^- + \text{AgI}\downarrow$$

Sodium azide was found to be of very limited solubility in nitriles other than acetonitrile, and tetraethylammonium azide was substituted in the general scheme. Tetraethylammonium azide was synthesized by interaction of aqueous solutions of barium azide and tetraethylammonium sulfate. For convenience, the tetraethylammonium azide was added as its solution in acetonitrile rather than as a solution in each individual nitrile. This was on the assumption that interaction of the N-(1-adamantyl)nitrilium hexafluoroantimonate with the dissolved azide would be considerably faster than nitrile exchange reactions (eq 3). This assumption was normally a good one, but in a few instances, notably in the formation of vinyl tetrazoles, the pmr spectrum of the crude reaction product showed a low intensity singlet methyl peak at τ 7.28, indicating the presence of small amounts of 1-(1-adamantyl)-5-



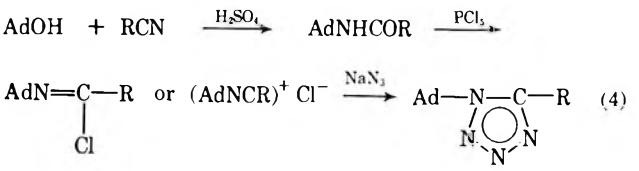
(3)

(1) D. N. Kevill and F. L. Weitl, *J. Amer. Chem. Soc.*, **90**, 6416 (1968).

(2) Although formulated as ionic, this could be fully or partially in the imide chloride form, Ad—N=C(Cl)R.

(3) P. von. R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 2700 (1961).

methyltetrazole. This contamination could be removed by recrystallization, but, for large-scale preparation of a single tetrazole, it would be desirable to dissolve the tetraethylammonium azide in the same nitrile as that participating in the prior solvolytic reaction. This silver ion assisted synthesis presents an alternative to the usually proposed pathway which would proceed *via* the amide[4] (eq 4).



(4)

The silver ion assisted formation from 1-adamantyl iodide has the advantage of by-passing the isolation of intermediates. It presents a very simple two-step sequence involving only the mixing of ingredients at room temperature over a period of minutes, followed by evaporation, partitioning between an organic solvent and water, and recrystallization. In particular, the mild conditions lead to reasonable yields of 5-vinyltetrazoles, incorporating readily polymerized acrylonitrile and substituted acrylonitriles.[5]

By treatment of the N-(1-adamantyl)nitrilium hexafluoroantimonate solution with water rather than with azide solution, good yields of N-(1-adamantyl)acrylamide and its α-methyl- and *trans*-β-phenyl-substituted derivatives were obtained. By reaction of 1-adamantyl chloroformate with sodium azide, in the absence of nitriles, 1-adamantyl azidoformate and 1-adamantyl azide have been prepared and characterized.

With the exception of 1-adamantyl azide, the pmr spectra in chloroform-*d* include, for the 15 adamantyl protons, a broad peak corresponding to 9 unresolved $\beta + \gamma$ protons and a second upfield broad peak corresponding to 6 unresolved δ protons. The 1-adamantyl azide shows separated signals for each of the three types of protons with a $J_{\beta\gamma}$ coupling constant of 2.6 Hz. The pmr spectral data fit into the general picture previously reported for other 1-substituted adamantanes.[6]

Certain 1-adamantyl and 1,5-substituted tetrazole derivatives have previously been found to exhibit useful biological activity. For example, 1-aminoadamantane (amantadine) and 1-hydrazoadamantane[7] possess antiviral activity, and pentamethylene-1,5-tetrazole (leptazole, "Cardiazole") has been used as a stimulant drug. There could well be examples of 5-substituted 1-(1-adamantyl)tetrazoles which possess appreciable biological activity.

(4) (a) For a brief discussion of the preparation and reactions of tetrazoles, see, for example, M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds," St. Martins Press, New York, N. Y., 1967, pp 399–403. (b) For preparations involving a more direct route to certain nitrilium salts, see L. A. Lee, E. V. Crabtree, J. U. Lowe, Jr., M. J. Czlesla, and R. Evans, *Tetrahedron, Lett.*, 2885 (1965).

(5) For relatively complex preparations leading to mixtures of 1-methyl-5-vinyltetrazole and 2-methyl-5-vinyltetrazole, see W. G. Finnegan, R. A. Henry, and S. Skolnik, (a) U. S. Patent 3,004,959 (1961) [*Chem. Abstr.*, **56** 15518 (1962)]; (b) U. S. Patent 3,062,880 (1962) [*Chem Abstr.*, **58**, 5705 (1963)]. Also, R. A. Henry, U. S. Patent 3,351,627 (1967) [*Chem. Abstr.*, **68**, 114605 (1968)]. These preparations involve introduction of the exocyclic double bond *after* construction of the tetrazole ring system.

(6) R. C. Fort, Jr., and P. von R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

(7) French Patent 1,491,581 (1967); *Chem. Abstr.*, **69**, 96074 (1968). See, also, H. U. Daeniker, *Helv. Chim. Acta*, **50**, 2008 (1967).

Experimental Section[8]

1-Adamantyl Iodide.—This compound was prepared from 1-adamantanol (Aldrich) by a modification of the method reported by Schleyer and Nicholas.[3] Hexane was found to be considerably superior to ether as a solvent for the extraction of the 1-adamantyl iodide. Carrying out the 1-adamantanol–hydriodic acid reaction,[3] decanting the aqueous layer, dissolving the residue in hexane, washing several times with water, drying over anhydrous magnesium sulfate, filtering, and evaporating gave approximately 95% yields of white crystals of 1-adamantyl iodide, mp 75–77° (lit.[3] mp 75.3–76.4°).

Stock Solution of Tetraethylammonium Azide.—A 100-ml portion of 10% aqueous solution of tetraethylammonium hydroxide (Eastman) was neutralized (litmus paper) with concentrated H_2SO_4. A solution of 13 g of barium azide (Alfa Inorganics 15% alcohol) in 50 ml of water was then slowly added until precipitation of barium sulfate ceased. After filtration the solution was concentrated at 50° with application of vacuum to a semisolid residue. A 400-ml portion of acetonitrile (Mallinckrodt "Nanograde") was added and the solution was azeotropically dried and concentrated by distillation to give a 50-ml stock solution.

1-(1-Adamantyl)-5-methyltetrazole. Procedure A.—A mixture of 1.0 g of sodium azide and 25 ml of acetonitrile was added to 2.0 g of 1-adamantyl chloroformate[1,9] and the mixture stirred for 30 min. The mixture was briefly heated to boiling and then allowed to stand at room temperature for a further 20 hr. The acetonitrile was evaporated under reduced pressure and the residue was extracted with benzene. The benzene solution was added to a silicic acid–Celite[10] column and successively eluted with hexane, benzene–hexane mixtures, and chloroform. The chloroform fraction gave 0.93 g (45%) of white solid: mp 127.5–129.0°; ir (KBr) 3.43, 3.50, 6.95, 7.26, 7.39, 7.45, 9.65, 12.00, 14.77 μ; pmr τ 7.28 (S, 3, CH_3), 7.68 (S, 9), 8.19 (S, 6).

Anal. Calcd for $C_{12}H_{18}N_4$: C, 66.03; H, 8.31; N, 25.67. Found: C, 66.11; H, 8.31; N, 25.52.

Procedure B.—A 2.20-g portion of silver hexafluoroantimonate (K and K Laboratories) was dissolved in 75 ml of acetonitrile and dried by azeotropic distillation; distillation was continued to give a residue of ~15 ml. To this residue was added, in a single portion, 1.50 g of 1-adamantyl iodide. An exothermic reaction occurred with precipitation of silver iodide. After about 2 min, 8 ml of the stock solution of NEt_4N_3 in CH_3CN was added and the solution adopted an orange-yellow color. After 30 min of shaking, Celite[10] was added, the mixture was filtered, the cake was washed well with CH_3CN, and the filtrate was evaporated to dryness under aspirator vacuum. The orange residue was partitioned between benzene and water, and the benzene layer was washed with water, dried with anhydrous $MgSO_4$, and evaporated under aspirator vacuum to give 1.25 g of a tan-colored residue. Recrystallization from petroleum ether (bp 60–100°) gave 0.89 g (71%) of white needles, mp 115–116°, followed by resolidification and second mp 126–127°; ir and pmr spectra were identical with those of the product from procedure A.

Anal. Found: C, 66.15; H, 8.35; N, 25.54.

Use of Procedure B to Prepare Other Tetrazoles.—With use of 1.50 g of 1-adamantyl iodide and with substitution of an appropriate nitrile as the solvent for the silver hexafluoroantimonate, several other 5-substituted 1-(1-adamantyl)tetrazoles were prepared. With the higher boiling nitriles, the azeotropic removal of water and concurrent concentration of the $AgSbF_6$ solution was achieved at reduced pressure. In each case, the NEt_4N_3 was added as its stock solution in acetonitrile.

1-(1-Adamantyl)-5-ethyltetrazole.—Nitrile was propionitrile (Eastman). The pmr spectrum of the crude product indicated it to be ~12% 1-(1-adamantyl)-5-methyltetrazole. A recrystallized yield of 0.38 g (29%) of white flakes gave mp 133.5–

(8) Melting points were taken in closed capillary tubes by use of calibrated Anschütz thermometers and a Büchi apparatus. Infrared spectra were obtained on a Beckman IR-8 using Styrofoam–KBr disks. Pmr spectra were recorded with a Varian A-60A spectrometer system, using chloroform-*d* as solvent. Microanalyses were by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Yields are based upon the appropriate 1-adamantyl reactant. Infrared spectra are outlined for three of the tetrazoles and one of the amides.

(9) W. L. Haas, E. V. Krumkalns, and K. Gerzon, *J. Amer. Chem. Soc.*, **88**, 1988 (1966).

(10) Celite is a kieselguhr supplied by the Johns-Manville International Corp., New York, N. Y.

134.5°; pmr τ 6.96 (q, 2, J = 7.5 Hz, CH_3CH_2–), 7.68 (S, 9), 8.20 (S, 6), 8.53 (t, 3, J = 7.5 Hz, CH_3CH_2–).

Anal. Calcd for $C_{13}H_{20}N_4$: C, 67.21; H, 8.68; N, 24.12. Found: C, 67.13; H, 8.79; N, 24.07.

Also, a second crop of 0.26 g (20%) gave mp 130–132°.

1-(1-Adamantyl)-5-propyltetrazole.—Nitrile was butyronitrile (Eastman). The crude residue (1.40 g), gave on recrystallization 0.90 g of white flakes (64%): mp 99–100.5°; pmr τ 7.02 (t, 2, J = 7 Hz, $CH_3CH_2CH_2$–), 7.69 (S, 9), 8.19 (broad, 6 + 2), 8.98 (t, 3, J = 7 Hz, $CH_3CH_2CH_2$–).

Anal. Calcd. for $C_{14}H_{22}N_4$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.07; H, 9.30; N, 22.69.

1-(1-Adamantyl)-5-isopropyltetrazole.—Nitrile was isobutyronitrile (Eastman). The crude residue (1.34 g) gave on recrystallization 0.87 g of white crystals, mp 156–170° (despite the wide melting point range, the pmr spectrum did not indicate any impurities). Two further recrystallizations from petroleum ether (bp 60–110°) and one from a petroleum ether (8 vol)–benzene (1 vol) mixture gave 0.61 g of white crystals (43%): mp 169–172°; pmr τ 6.52 [m, 1, J = 7 Hz, $(CH_3)_2CH$–], 7.69 (S, 9), 8.19 (S, 6), 8.57 (d, 6, J = 7 Hz, $(CH_3)_2CH$–).

Anal. Calcd for $C_{14}H_{22}N_4$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.08; H, 8.98; N, 22.82.

1-(1-Adamantyl)-5-phenyltetrazole.—Nitrile was benzonitrile (Velsicol Chemical Corp.). The 1.60 g of residue was recrystallized (0.22 g of tan solid: insoluble) to give 0.49 g of leafy white crystals, mp 154–157°. Two further recrystallizations from a mixture of petroleum ether (8 vol)–benzene (1 vol) gave 0.33 g (21%), mp 158–161°; ir 3.44, 3.51, 6.94, 7.38, 7.41, 7.46, 7.68, 8.44, 9.18, 9.32, 9.93, 12.08, 12.95, 13.48, 14.34, 14.51, 14.70 μ; pmr τ 2.55 (S with fine structure, 5, C_6H_5–), 7.82 (S, 9), 8.33 (S, 6).

Anal. Calcd for $C_{17}H_{20}N_4$: C, 72.82; H, 7.19; N, 19.98. Found: C, 72.81; H, 7.15; N, 20.02.

1-(1-Adamantyl)-5-vinyltetrazole.—Nitrile was acrylonitrile (Eastman). The 1.25 g of residue was recrystallized (some yellow insoluble material) to give 0.62 g of white flakes, mp 97–100° [pmr spectrum indicated presence of about 25% 1-(1-adamantyl)-5-methyltetrazole]. Three further recrystallizations from petroleum ether (bp 60–110°) gave 0.26 g (20%): mp 104–108°; ir 3.43, 3.51, 6.76, 6.96, 7.12, 7.32, 7.41, 7.69, 8.41, 9.11, 9.62, 10.19, 10.58, 12.01, 13.00, 14.36, 15.01 μ; pmr τ 3.07 + 3.59 + 4.21 (AMX vinylic system, 3, J_{AM} = 17.0 Hz, J_{AX} = 10.5 Hz, J_{MX} = 2.1 Hz, respectively the α-H, *trans*[11]-β-H, *cis*[11]-β-H), 7.68 (S, 9), 8.19 (S, 6).

Anal. Calcd for $C_{13}H_{18}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 67.69; H, 7.82; N, 24.23.

1-(1-Adamantyl)-5-(α-methylvinyl)tetrazole.—Nitrile was methacrylonitrile (Eastman). The pmr spectrum of the 1.34 g of crude brown residue indicated the presence of about 10% 1-(1-adamantyl)-5-methyltetrazole. Recrystallization (some insoluble black tar) gave 0.59 g of tan crystals, mp 135–150°. Three further recrystallizations from petroleum ether (bp 60–110°) gave 0.20 g of tan crystals (14%): mp 148–151°; pmr τ 4.41 + 4.72 (MX system with fine structure, 2, respectively *trans*[11]-β-H and *cis*[11]-β-H), 7.68 (S, 9), 7.83 (S with fine structure, 3, CH_3–), 8.24 (S, 6).

Anal. Calcd for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.83; H, 8.25; N, 23.00.

1-(1-Adamantyl)-5-(*trans*-β-phenylvinyl)tetrazole.—Nitrile was cinnamonitrile (Eastman). An additional step was a treatment, prior to evaporation, of the dried benzene solution with carbon black (Norite). The crude tetrazole was recrystallized not from petroleum ether but from a petroleum ether (bp 60–110°) (10 vol)–benzene (1 vol) mixture. Obtained was 0.88 g of tan crystals (49%): mp 163.5–164.5°; pmr τ 2.15 (d, 1, J = 15.8 Hz, vinylic), *ca.* 2.54 (complex overlapping series, 5, C_6H_5–), 2.89 (d, 1, J = 15.8 Hz, vinylic), 7.62 (S, 9), 8.17 (S, 6).

Anal. Calcd for $C_{19}H_{22}N_4$: C, 74.47; H, 7.24; N, 18.28. Found: C, 74.85; H, 7.09; N, 18.17.

N-(1-Adamantyl)acrylamide.—A 2.3-g portion of $AgSbF_6$ was dissolved in 75 ml of acrylonitrile and the solution was distilled until a residue of 10 ml remained. To this residue at room temperature was added 1.5 g of 1-adamantyl iodide followed, after shaking for 5 min, by 10 ml of an acetonitrile (4 vol)–water (1 vol) mixture. After addition of Celite[10] and filtration, the cake was washed with CH_3CN, and the total solution was evaporated to dryness to leave a white residue which was partitioned between benzene and water. The benzene layer was washed several times with water, dried with anhydrous $MgSO_4$, and evaporated to give 1.11 g of white residue. Recrystallization from petroleum ether (60–110°) gave 0.88 g of white needles (75%): mp 148–148.5°; ir 3.08, 3.26, 3.43, 3.51, 6.10, 6.22, 6.51, 6.94, 7.15, 7.40, 7.48, 7.70, 7.91, 8.08, 8.46, 8.92, 9.18, 9.42, 10.12, 10.59, 11.08, 12.41, 13.72 μ; pmr τ 3.81 + 3.91 + 4.44 (3 vinylic protons,[12] respectively *trans*[11]-β-H, α-H, and *cis*[11]-β-H), *ca.* 4.5 (broad, 1, –NH–), 7.94 (S, 9), 8.30 (S, 6).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.03; H, 9.33; N, 6.82. Found: C, 76.17; H, 9.54; N, 6.63.

N-(1-Adamantyl)methacrylamide.—Prepared as was N-(1-adamantyl)acrylamide with substitution of methacrylonitrile for acrylonitrile. A minor modification was the addition of 1 ml of pyridine concurrent with the 10 ml of aqueous acetonitrile. A crude residue of 1.18 g gave on recrystallization 0.51 g of white crystals (41%): mp 102–104°; pmr τ 4.44 (S with fine structure, 1, *trans*[11]-β-H), *ca.* 4.57 (broad, 1, –NH–), 4.77 (S with fine structure, 1, *cis*[11]-β-H), 7.94 (S, 9), 8.09 (S with fine structure, 3, CH_3–), 8.30 (S, 6).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.56; H, 9.74; N, 6.40.

A second crop of 0.55 g (44%) was recovered from the recrystallization mother liquor, mp 98–102°.

N-(1-Adamantyl)-*trans*-cinnamamide.—Prepared as was N-(1-adamantyl)methacrylamide but with substitution of 25 ml of cinnamonitrile for 75 ml of methacrylonitrile. Recrystallization was from a (bp 60–110°) petroleum ether (4 vol)–benzene (1 vol) mixture rather than from petroleum ether (bp 60–110°). Obtained was 0.25 g of white crystals (16%), mp 196–199° dec. Addition of petroleum ether to the mother liquor gave a further 0.90 g of white crystals (56%), mp 196–198° dec, for a total yield of 72%: pmr τ 2.44 (d, 1, J = 15.7 Hz, *trans*[11]-β-H), *ca.* 2.62 (complex overlapping series, 5, C_6H_5–), 3.66 (d, 1, J = 15.7 Hz, α-H), 7.91 (S, 9), 8.28 (S, 6).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.96; H, 8.52; N, 4.91.

1-Adamantyl Azidoformate.[13] **Procedure A.**—To 0.5 g of sodium azide in a mixture of 3.5 g of water and 7.5 g of acetone was added 1.0 g of 1-adamantyl chloroformate. The mixture was stirred for 48 hr at room temperature and 50 ml of water was then added. A colorless oil separated and this was combined with four 25-ml ether extracts of the aqueous soluton. The ether solution was dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was dissolved in benzene and eluted from a silicic acid–Celite[10] column. Using hexane, a small amount of 1-adamantyl chloride was obtained, followed by a trace of 1-adamantyl azide (ir included 4.80 μ ($-N_3$), no C=O or OH peaks present). A benzene (1 vol)–hexane (1 vol) mixture was then used to elute 0.54 g (52%) of white, crystalline 1-adamantyl azidoformate: mp 43–44° (lit.[15] pale yellow oily liquid); ir 3.44, 3.51, 4.59, 4.70, 5.86, 6.92, 8.24, 9.10, 9.61, 10.42, 10.56, 11.31, 12.32, 13.15, 13.33 μ; pmr τ 7.85 (S, 9), 8.32 (S, 6).

Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.80; H, 6.78; N, 19.18.

Procedure B.—A 0.5-g portion of 1-adamantyl chloroformate was dissolved in 15 ml of methanol containing 0.33 g of sodium azide. Precipitation of sodium chloride was accompanied by an evolution of gas. After standing overnight, the methanol was removed by evaporation under aspirator vacuum and the residue was extracted with hexane. Column chromatography, as in procedure A, yielded 0.25 g (48%) of white crystalline 1-adamantyl azidoformate, mp 42–43°.

1-Adamantyl Azide.—A 4.0-g portion of 1-adamantyl chloroformate was added to a mixture of 20 ml of ether, 20 ml of water, and 8.0 g of sodium azide. The mixture was stirred for 2 weeks and then the ether layer was separated, dried with anhydrous

(11) In describing the pmr spectra of vinylic compounds, *cis* and *trans* are relative to the α hydrogen or, for α-methyl derivatives, the α-methyl group.

(12) Splitting pattern of vinyl protons identical with that illustrated for N-isopropylacrylamide: N. S. Bhacca, L. F. Johnson, and J. L. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, spectrum 468.

(13) Although there are two references to 1-adamantyl azidoformate in the literature,[14,15] it does not appear to have been prepared in pure form and characterized.

(14) W. V. Curran and R. B. Angier, *Chem. Commun.*, 563 (1967); *J. Org. Chem.*, **34**, 3669 (1969).

(15) K. Gerzon and E. V. Krumkalns, U. S. Patent 3,369,041 (1968).

Na_2SO_4, and evaporated under reduced pressure. The residue was extracted with hexane and the hexane solution was eluted from a silicic acid–Celite[10] column by use of a hexane (3 vol)–benzene (7 vol) mixture. Evaporation of the second fraction gave 0.20 g (6%) of white crystalline 1-adamantyl azide: mp 82–83°; ir 3.43, 3.51, 4.80, 6.92, 8.02, 9.49, 11.32, 12.33, 13.67, 14.82 μ; pmr τ 7.84 (S, 3, γ-H), 8.19 (d, 6, J = 2.6 Hz, β-H), 8.30 (6, δ-H).

Anal. Calcd for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53; N, 23.59. Found: C, 67.56; H, 8.42; N, 23.62.

Evaporation of the first and third fractions gave a trace of 1-adamantyl chloride (identified by infrared spectrum) and 0.3 g of 1-adamantyl azidoformate, mp 42–43°, respectively. A large fourth fraction had an infrared spectrum indicating that it was 1-adamantanol.

Registry No.—1-(1-Adamantyl)-5-methyltetrazole, 24886-62-2; 1-(1-adamantyl)-5-ethyltetrazole, 24940-56-5; 1-(1-adamantyl)-5-propyltetrazole, 24886-63-3; 1-(1-adamantyl)-5-isopropyltetrazole, 24886-64-4; 1-(1-adamantyl)-5-phenyltetrazole, 24886-65-5; 1-(1-adamantyl)-5-vinyltetrazole, 24886-66-6; 1-(1-adamantyl)-5-(α-methylvinyl)tetrazole, 24886-67-7; 1-(1-adamantyl)-5-(*trans*-β-phenylvinyl)tetrazole, 24886-68-8; N-(1-adamantyl)acrylamide, 19026-83-6; N-(1-adamantyl)methacrylamide, 24886-70-2; N-(1-adamantyl)-*trans*-cinnamamide, 24886-71-3; 1-adamantyl azidoformate, 19386-43-7; 1-adamantyl azide, 24886-73-5.

A Reinvestigation of the Mannich Reaction of 4-Nitrophenylacetic Acid and 2,4-Dinitrophenylacetic Acid[1]

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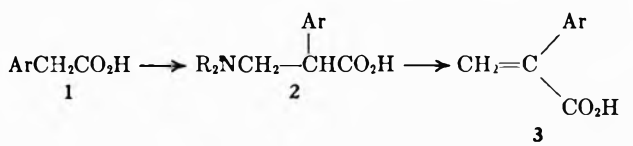
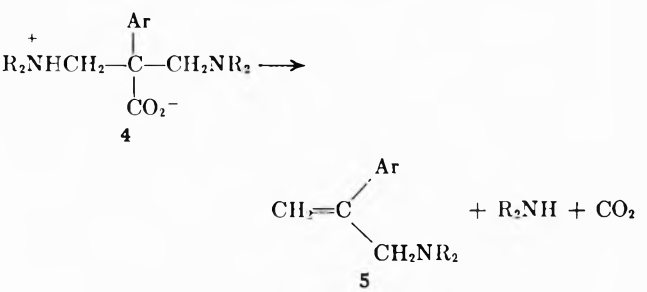
The reaction of 4-nitrophenylacetic acid with piperidine and formaldehyde gives rise to α-(N-piperidinomethyl)-4-nitrostyrene (**5**) *via* a slow second Mannich condensation of the intermediate α-(4-nitrophenyl)-β-(N-piperidino)propionic acid (**2**) and subsequent decarboxylative deamination of **4**. 2,4-Dinitrophenylacetic acid also undergoes mono- and bisaminomethylation under Mannich conditions; however, the intermediate amino acids **6** and **7** spontaneously decarboxylate to yield the monoamine **8** and diamine **9**. The elimination reactions of **2** have been studied over the pH range of 1–11. In acidic medium, deamination occurs to yield theacrylic acid **3**; under basic conditions, decarboxylative deamination predominates to yield 4-nitrostyrene. Above pH 6, **2** also undergoes the retro Mannich reaction.

Although reports due to Mannich and a few later workers indicate that α-methylene functions of certain activated carboxylic acids can undergo condensation to incorporate two $-CH_2NR_2$ groups,[3] a detailed study of these reactions has not been made. Our interest in this topic arose from an attempt to repeat Mannich's synthesis of α-(4-nitrophenyl)acrylic acid. This procedure involves reaction of the piperidinium salt of 4-nitrophenylacetic acid with formaldehyde in aqueous solution to yield α-(4-nitrophenyl)-β-(N-piperidino)-propionic acid (**2**) which is deaminated by heating in aqueous solution kept neutral by periodic addition of dilute hydrochloric acid.[4]



Ar– = 4-nitrophenyl; R_2N– = piperidyl

In the first step of this sequence, we have isolated a 29% yield of α-(N-piperidinomethyl)-4-nitrostyrene (**5**) in addition to the β-amino acid **2** (65% yield). This styrene apparently arises by aminomethylation of **2** to yield **4**, which then undergoes decarboxylative deamination as shown in the following reaction scheme.



Ar– = 4-nitrophenyl; R_2N– = piperidyl

This conclusion is supported by observation of the β-amino acid **2** as an intermediate in the formation of **5**.[5] Stepwise loss of carbon dioxide and piperidine[6] is ruled out since 2-(4-nitrophenyl)-1,3-di(N-piperidino)propane was inert under the reaction conditions.

In contrast to the reaction of 4-nitrophenylacetic acid, Mannich and Stein reported that 2,4-dinitrophenylacetic acid reacts with piperidine and formaldehyde to yield only 2-(2,4-dinitrophenyl)-1,3-di(N-piperidino)-propane (**9**).[4] However, repetition of this reaction in dilute aqueous ethanol solution at 31° resulted in appreciable amounts of the monoamine **8** and 2,4-dinitrotoluene in addition to the diamine **9**. Decarboxylation of the piperidinium salt of 2,4-dinitrophenylacetic acid occurred readily under these conditions. Since Kermack and Muir had reported formation of both

(1) Presented at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

(2) Abstracted in part from the M. S. Thesis of E. Hertz, presented to the Department of Chemistry, Villanova University, April 1968.

(3) F. F. Blick, *Org. React.*, **1**, 310 (1942); B. Reichert, "Die Mannich Reaktion," Springer-Verlag, Berlin, 1959, p 41.

(4) C. Mannich and L. Stein, *Ber.*, **58B**, 2659 (1925).

(5) It should be noted that decarboxylative deamination of postulated β-amino acid intermediates under Mannich conditions has been invoked previously, *e.g.*, (a) C. A. Grob and P. W. Schiess, *Angew. Chem. Int. Ed. Engl.*, **6**, 1(1967), and references cited therein; (b) H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **31**, 4146 (1966).

(6) B. B. Thompson, "Some Studies in the Mannich Reaction," Ph.D. Thesis, The University of Mississippi, 1963.

TABLE I

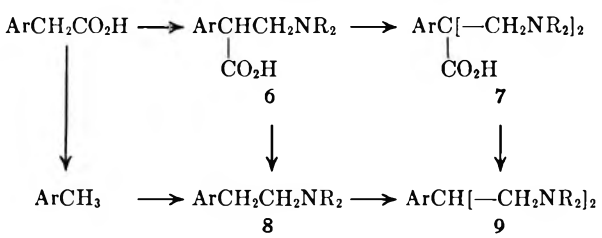
pH DEPENDENCE OF THE VARIOUS REACTIONS OF α-(4-NITROPHENYL)-β-(N-PIPERIDINO)PROPIONIC ACID IN AQUEOUS SOLUTION

						% yield of various products				
						Deamination	Decarboxylative deamination		Mannich reaction	
Run	Mol of **2**	Mol of HCl	pH range	Temp, °C	Time, hr	**3**	**10**	**11**	**1**	**5**
1	0.25	*a*	11–11[b]	100	9	0	0	45 9	15.9	12.6
2	0.1	c	11–9	97	3	0	3.1	27 3	22.9	18.7
3	0.05	*c*	9–9	85	3	1	0.6	17 0	13.1	13.1
4	0.05	0	6–8	100	3	6 3	25.2	20 8	10.6	12.0
5	0.05	*d*	4–6	100	3	*e*	23.6	*e*	*e*	*e*
6	0.05	0.0375	3–5	100	3	~1	7.8	30 0	~1	Trace
7	0.05	0.05	1–3.5	100	3	45.7[f]	0	8 9	~1[g]	Trace

[a] Two equivalents of piperidine (instead of HCl) was added at the beginning of the reaction. [b] Ranges denote the pH at the beginning (at 80°) and at the end of the reaction (except for run 5). [c] One equivalent of piperidine was employed. [d] The pH was kept in the 4–6 range by adding 1 *N* HCl every 5–10 min. [e] Not investigated. [f] Several runs under similar conditions gave **3** in yields of 45.7–60.1%. [g] A 3.3% yield of di(N-piperidino)methane was also obtained from this reaction.

8 and **9** from the reaction of 2,4-dinitrotoluene with piperidine and formaldehyde in refluxing ethanol solution,[7] it was of interest to determine the relative involvement of the intermediates shown in Scheme I for the Mannich reaction of 2,4-dinitrophenylacetic acid.

SCHEME I



Ar– = 2,4-dinitrophenyl; R_2N– = piperidyl

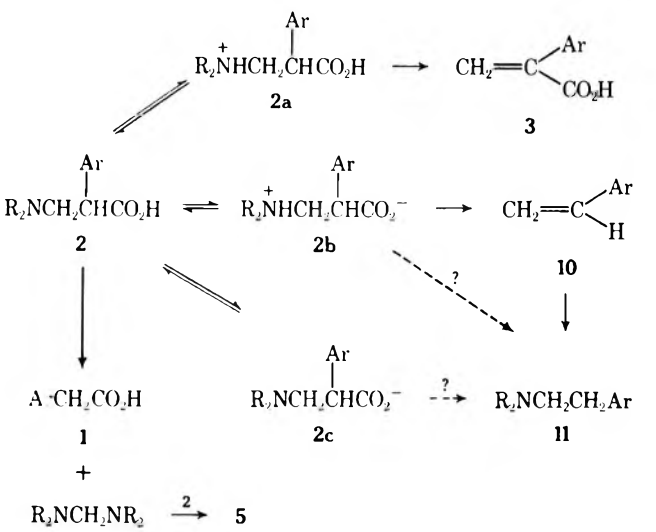
Since aminomethylation of the monoamine **8** occurred at a lower rate than the formation of **8** from 2,4-dinitrotoluene in refluxing ethanol solution and since reaction of 2,4-dinitrotoluene with piperidine and formaldehyde was undetectable at 31°, both 2,4-dinitrotoluene and the monoamine **8** can be ruled out as intermediates in the Mannich reaction of 2,4-dinitrophenylacetic acid in dilute solution at room temperature. This implicates intermediate **7** as the source of diamine **9** and the β-amino acid **6** as the precursor to the monoamine **8**. Although **8** and **9** may result by decarboxylative deamination of the nonisolable amino acids **6** and **7**, followed by reamination of the intermediate 2,4-dinitrostyrene and α-(N-piperidinomethyl)-2,4-dinitrostyrene, the alternate possibility involving decarboxylation of **6** and **7** cannot be eliminated.

In the course of this study, several alternate, pH-dependent pathways were observed for decomposition of α-(4-nitrophenyl)-β-(N-piperidino)propionic acid (**2**) in aqueous solution. Although the acrylic acid **3** could be obtained in up to 60% yield under carefully controlled conditions, it was accompanied by 4-nitrostyrene (**10**), 1-(4-nitrophenyl)-2-(N-piperidino)ethane (**11**), 4-nitrophenylacetic acid (**1**), and α-(N-piperidinomethyl)-4-nitrostyrene (**5**) (Scheme II). The yields of these products as a function of the pH of the reaction medium are listed in Table I.

It should be noted that the yield of α-(4-nitrophenyl)-

(7) W. O. Kermack and W. Muir, *J. Chem. Soc.*, 300 (1933).

SCHEME II



Ar– = 4-nitrophenyl; R_2N– = piperidyl

acrylic acid (**3**) decreases with increasing pH while the yield of 4-nitrostyrene (**10**) follows the opposite trend. Since the isoelectric point for the amino acid **2** occurs at pH 6.0, it is apparent that the protonated species **2a** predominating below pH 6, gives rise to the acrylic acid, while the zwitterion **2b** predominating above pH 6 is the percursor to 4-nitrostyrene. The sharp decrease in yield of 4-nitrostyrene above pH 8 is largely the result of secondary reaction with piperidine to form the amine **11**.[8] Note that **11** may also arise by decarboxylation of either the anion **2c** or the zwitterion **2b**.[9]

The formation of 4-nitrophenylacetic acid at high pH is undoubtedly due to a retro Mannich reaction resulting from nucleophilic displacement of the 4-nitrophenylacetate group from the β-amino acid **2** by piperidine.[10] The other product of this reaction, di-(N-piperidino)methane (or species derived therefrom) apparently effects aminomethylation of the amino acid

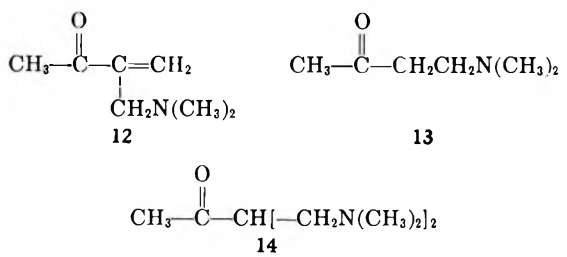
(8) This reaction occurs readily in ethanol solution under similar conditions: W. J. Dale and G. Buell, *J. Org. Chem.*, **21**, 45 (1956).

(9) Ulrich and Sayigh (ref 5b) report that the amine resulting from the reaction of α-(4-nitrophenyl)-*cis*-2,5-dimethoxycinnamic acid with piperidine must form solely by decarboxylation of the β-amino acid intermediate, since the stilbene formed by decarboxylative deamination is inert to reamination.

(10) B. B. Thompson, *J. Pharm. Sci.*, **57**, 715 (1968), and references cited therein.

2,[10,11] to yield **4**, which then undergoes decarboxylative deamination to provide α-(N-piperidinomethyl)-4-nitrostyrene (**5**).

The variety of reactions accompanying aminomethylation of the nitro-substituted phenylacetic acids prompts extension of this study to other systems. Preliminary results from the reaction of acetoacetic acid with dimethylamine and formaldehyde indicate formation of methyl α-(dimethylaminomethyl)vinyl ketone **12**[12] in addition to the monoamine **13** and diamine **14** reported by Mannich and Curtaz.[13]



12 **13**

14

Experimental Section[14]

Mannich Reaction of 4-Nitrophenylacetic Acid.—The crude mixture from reaction of the piperidinium salt of 4-nitrophenylacetic acid with aqueous formaldehyde (1 mol of each, 0.1 mol excess of piperidine) at room temperature[4] for 4 days was filtered under suction to remove the crystalline **2**. The filtrate was extracted with chloroform, and the extract was washed with water, dried ($MgSO_4$), filtered, and evaporated on the steam bath at aspirator vacuum. The resulting oil was purified by vacuum distillation. After a forerun of di(N-piperidino)methane, bp 62° (0.7 mm) [lit.[15] bp 75–81° (4 mm)], 71.7 g (29.1% yield) of amber α-(N-piperidinomethyl)-4-nitrostyrene (**5**), bp 144–152° (0.5 mm), was obtained:[16] nmr ($CDCl_3$) δ 1.4 (m, 6, piperidine ring), 2.4 (m, 4, pip ring), 3.3 (s, $-CH_2NR_2$), 5.4 and 5.6 (d, d, J = 2 Hz, $H_2C{=}C$), 7.7 and 8.15 (d, d, J = 9 Hz, 4-nitrophenyl).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.02; H, 7.15; N, 11.28.

Reaction of **2** with piperidine and formaldehyde under conditions similar to those just cited also resulted in a mixture of **5** and di(N-piperidino)methane.

Preparation of 2-(4-Nitrophenyl)-1,3-di(N-piperidino)propane.—A mixture of 4.92 g (0.02 mol) of **5** and 10 ml of piperidine was heated under reflux at 120–145° for 20 hr. The remaining piperidine was removed on a rotary evaporator (aspirator vacuum). The crude product was recrystallized 3 times from ethanol to yield 3.4 g (51.5%, not optimum[16]) of pale yellow crystals: mp 81.5–83.5°; nmr ($CDCl_3$) δ 1.45 (m, 12, pip rings), 2.0–2.7 (m, 8, pip rings) overlapping the absorptions for the four $-CH_2NR_2$ protons, 2.75–3.5 (m, ArCH–) and 7.35 and 8.15 (d, d, J = 8.5 Hz, 4-nitrophenyl).

Anal. Calcd for $C_{19}H_{29}N_3O_2$: C, 68.85; H, 8.82; N, 12.68. Found: C, 69.06; H, 8.82; N, 12.70.

Aminomethylation of 2,4-Dinitrotoluene.—Reaction of 2,4-dinitrotoluene with piperidine and formaldehyde (equimolar) in refluxing ethanol was carried out according to Kermack and Muir.[7] Diamine **9** was obtained in 21% yield by successive evaporation and crystallization of the crude ethanol solution. Concentration of the mother liquor gave a red-brown oil which was dissolved in anhydrous ether. Saturation of this solution with HCl resulted in the hydrochloride of **8** which was removed by suction filtration and triturated with acetone and ether. The light tan powder was obtained in 58.7% yield.

Anal. Calcd for $C_{13}H_{18}N_3O_4Cl$: C, 49.45; H, 5.75; N, 13.31; Cl, 11.23. Found: C, 49.28; H, 5.82; N, 13.10; Cl, 11.14.

The free amine **8**, obtained by treatment of the hydrochloride with dilute KOH solution, exploded at 165° (high vacuum) on attempted distillation. The nmr spectrum of **8** ($CDCl_3$) has peaks at δ 1.5 (m, 6, pip ring), 2.45 (m, 4, pip ring), 2.7 and 3.2 (t, t, J = 7 Hz, $-NCH_2CH_2Ar$) plus the three-proton pattern for the 2,4-dinitrophenyl group. The diamine **9** possesses absorptions ($CDCl_3$) at δ 1.35 (m, 12, pip rings), 2.0–2.7 (m, 8, pip rings), which mask a complex four-proton pattern for the $-CH_2NR_2$ protons, and 3.5–4.3 (m, ArCH–) in addition to the expected peaks for the 2,4-dinitrophenyl group.

Relative Reactivity of 2,4-Dinitrophenylacetic Acid and 2,4-Dinitrotoluene with Piperidine and Formaldehyde.—A solution of 5.6 g of 2,4-dinitrophenylacetic acid and 2.12 g of piperidine (0.025 mol of each) in 450 ml of 95% ethanol at 31.5° was mixed with a solution of 3.65 ml (0.05 mol) of 37.7% formaldehyde and 2.12 g (0.025 mol) of piperidine in 20 ml of 95% ethanol at the same temperature (constant-temperature bath). After 6 hr the mixture was poured into 1500 ml of water and extracted with chloroform. The extract was reserved. The basic aqueous fraction was neutralized with dilute HCl and extracted with chloroform. This extract was dried ($MgSO_4$), filtered, and evaporated to yield 0.41 g (7.25%) of 2,4-dinitrophenylacetic acid. The reserved chloroform extract which contained monoamine **8**, diamine **9**, and 2,4-dinitrotoluene was shaken with dilute HCl to remove the amines. The chloroform layer was then washed with water, dried ($MgSO_4$), and evaporated to yield 0.58 g (12.7%) of 2,4-dinitrotoluene. The acidic aqueous layer was neutralized with KOH pellets and extracted with ether. The extract was dried ($MgSO_4$) and evaporated. Crystallization of the crude product from ethanol yielded 3.35 g (35.5%) of diamine **9** and 1.18 g (16.9%) of red-brown oil, identified by nmr as quite pure monoamine **8**.[17]

A similar run conducted with 2,4-dinitrotoluene and 0.025 mol of acetic acid in place of 2,4-dinitrophenylacetic acid resulted in 87% recovery of 2,4-dinitrotoluene. The only amine isolated was di(N-piperidino)methane. The same results were obtained when acetic acid was omitted.

Decarboxylation of 2,4-dinitrophenylacetic acid with piperidine in the absence of formaldehyde was examined under similar conditions. When the reaction mixture was poured into water, 0.69 g (24.4% yield) of 2,4-dinitrotoluene was isolated (~0.3 g was probably lost owing to solubility in water–ethanol).

Elimination Reactions of α-(4-Nitrophenyl)-β-(N-piperidino)-propionic Acid (2). General Procedure for Reactions Listed in Table I.—The indicated amount of **2** plus 10 ml of water/0.01 mol of **2** was placed in a three-necked round-bottom flask fitted with a heating mantle, magnetic stirrer, and reflux condensor. The pH was controlled by addition of 1 *N* HCl or piperidine. The reaction mixture was then heated at the specified temperature for the time indicated. After cooling and basifying with dilute KOH solution, 4-nitrostyrene and the amines were removed by ether extraction. Treatment of this extract with dilute HCl resulted in an ether solution of 4-nitrostyrene and an aqueous solution of the amine hydrochlorides. The free amines were isolated from aqueous solution by treatment with KOH solution, followed by ether extraction. The extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. The yields of amines were conveniently determined by nmr analysis of the crude mixtures. Crystalline α-(4-nitrophenyl)acrylic acid (**3**) and/or 4-nitrophenylacetic acid (**1**) were obtained by acidifying the initial basic aqueous fraction to pH 1 with concentrated HCl and cooling overnight. The yields were determined by nmr.

The optimum yield of **3** was achieved under the conditions indicated in run 7. The reaction time of 3 hr was optimum. When 2 equiv of HCl was employed or when the reaction was scaled up to 0.2 mol, the yield dropped sharply. Crude **3**, isolated by acidifying the reaction mixture to pH 1 with concentrated HCl and cooling overnight, contained no 4-nitrophenylacetic acid. After recrystallization from acetone–methylene chloride (decolorizing carbon), **3** was collected and dried *in vacuo*:

(11) W. L. Nobles and N. D. Potti, *J. Pharm. Sci.*, **57**, 1097 (1968).

(12) H. J. Spinelli, unpublished results, this laboratory.

(13) C. Mannich and K. Curtaz, *Arch. Pharm.* (Weinheim), **264**, 741 (1926).

(14) The nmr spectra were obtained with a Varian A-60 spectrometer using TMS as the internal standard. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were obtained with a liquid bath and are uncorrected.

(15) A. Binz and L. H. Pence, *J. Amer. Chem. Soc.*, **61**, 3134 (1939).

(16) Caution: The above reaction mixture and α-(N-piperidinomethyl)-4-nitrostyrene are severe vessicants.

(17) When 2,4-dinitrophenylacetic acid was treated with piperidine and formaldehyde (0.03: 0.06:0.06 mol ratio) in 200 ml of ethanol for 2 days at room temperature, a 66% yield of **9**, a 14% yield of **8**, and a trace of 2,4-dinitrotoluene were realized.

mp 174.5–177° (lit.[4] mp 176–177°; nmr (d_6-acetone) 6.2 and 6.6 (s, s, H_2C=C) and 7.8 and 8.25 (d, d, J = 9 Hz, 4-nitrophenyl) as well as absorption for the acidic hydrogen.

Registry No.—**1**, 104-03-0; **2**, 13797-13-2; **5**, 24886-58-6; **8**, 24886-59-7; **8** HCl, 24886-60-0; 2,4-dinitrophenylacetic acid, 643-43-6; 2-(4-nitrophenyl)-1,3-di(N-piperidino)propane, 24886-61-1.

Acknowledgment.—The authors wish to thank Dr. J. J. Cawley and Dr. W. W. Zajac, Jr. for helpful suggestions during the course of this work.

Photochemical Reactions of Phenacyl- and Benzylsulfonium Salts[1]

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Phenacylsulfonium tetrafluoroborates (**1**, **5**, **7**, **9**, and **11**) on irradiation afford products resulting from homolytic cleavage of the phenacyl carbon–sulfur bond. Benzylsulfonium tetrafluoroborates (**13**, **22**, **24**, **29**, and **32**) on irradiation afford products resulting from both homolytic and heterolytic cleavage of the benzyl carbon–sulfur bond where the heterolytic cleavage is the major pathway. β-Keto sulfonium fluoroborates (**44** and **46**) on irradiation in methanol are converted to polymeric products. Syntheses are described for all photochemical products previously unreported.

The photolysis of dimethylphenacylsulfonium bromide in water was recently reported.[3] Irradiation of the salt in methanol for 1 hr in these laboratories also produced acetophenone (51%) and phenacyl bromide (<5%) but no significant amount of *p*-bromodibenzoylethane which was reported to be the major product (25%) on irradiation in water.[3] Furthermore, irradiation of phenacyl bromide in methanol under similar conditions for 1 hr produced acetophenone (41%) indicating that acetophenone must arise in part, if not completely, from phenacyl bromide as an intermediate.[4] In view of this involvement of bromide ion in the photolysis, the tetrafluoroborate salt of dimethylphenacylsulfonium ion and other aroylsulfonium ions was irradiated in order to prevent anion involvement whether the cleavage of the carbon–sulfur bond was heterolytic or homolytic. The nonpolymeric products formed are listed in Table I.

Acetophenone (**2**) was the sole product from photolysis of **1** in methanol, but the coupling product **3** was observed in *t*-butyl alcohol and acetonitrile and the rearrangement product **4** was observed in low yield in *t*-butyl alcohol. In similar fashion **5**, **7**, and **9**, on irradiation in methanol, were converted to **6**, **8**, and **10**, respectively. Tetrafluoroborate salt **11** follows a similar reaction course in methanol and water.

The presence of the phenacyl dimer **3** in solvents other than methanol is in line with the increased difficulty of abstraction of a hydrogen atom by a radical from the other solvents.[5] An excited-state solvolysis of the sulfonium salts in methanol to form the corresponding α-methoxy ketone can not be discarded since α-methoxyacetophenone rapidly photolyzed in methanol to form **2**.[6] On the other hand, α-hydroxyacetophenone gave no monomeric products on irradiation in water and thus would not appear to be an intermediate in the irradiation of **1** or **11** in water. This would appear to eliminate an excited-state solvolysis as the reaction pathway of the BF_4^- salts in water.

The isolation of **12** from the photolysis of **11** rules out a Norrish type II process for the formation of **2**[7] since the $C_3H_7CH{=}S^+C_4H_9$ formed in such a process would be converted to $C_3H_7CH(OR)CHSC_4H_9$ (R = CH_3 in methanol, R = H in water).

The data from irradiation of the BF_4^- salts are most consistent with a radical pathway involving initial homolytic cleavage to the phenacyl radical[8,9] and the dialkylsulfinium cation radical.[10–12] Diarylsulfinium cation radicals are probably involved in the photolytic decomposition of triarylsulfonium salts.[14] The dimethylsulfinium cation radical formed from photolysis of **1** (in *t*-butyl alcohol) may lose H^+ to form $\cdot CH_2CSH_3$

(1) This research has been supported by National Science Foundation Grant No. GP-7831 and by National Institutes of Health Grant No. AI-09300.

(2) National Institutes of Health Predoctoral Fellow, 1965–1968.

(3) T. Laird and H. Williams, *Chem. Commun.*, 561 (1969).

(4) Irradiation of phenacyl chloride in ethanol affords only acetophenone (53%); J. C. Anderson and C. B. Reese, *Tetrahedron Lett.*, 1 (1962).

(5) (a) V. K. Schwetlich, R. Karland and J. Jentzsch, *J. Prakt. Chem.*, **22**, 113 (1963), report the rate of hydrogen atom abstraction by *t*-butoxy radicals to decrease in the following order: $CH_3OH > CH_3CN > (CH_3)_3OH$. (b) Water is known to be a poor hydrogen atom donor: A. Becket and G. Porter, *Trans. Faraday Soc.*, **59**, 2039 (1963).

(6) R. B. LaCount and C. E. Griffin, *Tetrahedron Lett.*, 1549 (1965), report that photolysis of α-methoxyacetophenone in benzene gives 3-phenyl-3-oxethanol (10% yield). P. Yates and A. G. Szabo, *ibid.*, 485 (1965), report obtaining the same product (29% yield) in benzene on irradiation for 12 hr. A detailed study of the photochemistry of α-alkoxyacetophenones has appeared recently: F. D. Lewis and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 311 (1970).

(7) This assumes **2** and **12** are formed in the same reaction process.

(8) The study by R. L. Huang and P. Williams, *J. Chem. Soc.*, 2637 (1958), indicates that phenacyl radicals are probably more reactive than benzyl radicals.

(9) Acetophenone, one of the products of the photolytic decomposition of dimethylsulfonium phenacylide [B. M. Trost, *J. Amer. Chem. Soc.*, **89**, 138 1967)] and diazoacetophenone [D. O. Cowan, *et al.*, *J. Org. Chem.*, **29**, 1922 (1964)] in alcohols, presumably arose *via* phenacyl radicals formed from hydrogen atom abstraction by benzoyl carbene.

(10) Cation radicals of this type have been produced by the oxidation of aryl sulfides in concentrated H_2SO_4:[11] H. J. Shine, *et al.*, *J. Org. Chem.*, **32**, 1901 (1966), and references cited therein; A. Zweig, *et al.*, *Tetrahedron Lett.*, 1821 (1963).

(11) Reviews on the formation of sulfur cation radicals have appeared: (a) U. Schmidt, in "Organosulfur Chemistry," M. J. Jannsen, Ed., Interscience Publishers, New York, N. Y., 1967 p 75; (b) H. J. Shine, in ref 11a, p 93

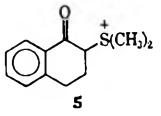
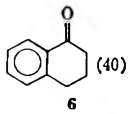
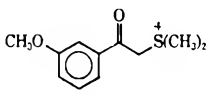
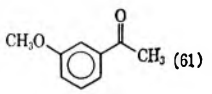
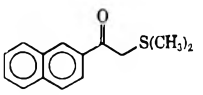
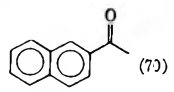
(12) Although the anodic oxidation of dialkyl sulfides is reported to produce a single wave representing removal of two electrons,[13] Zweig, *et al.*, (ref 10) cite convincing evidence for formation of the cation radical from dithiohydroquinone dimethyl ether by electrochemical oxidation.

(13) M. M. Nicholson, *J. Amer. Chem. Soc.*, **76**, 2539 (1954); V. Drushel and J. F. Miller, *Anal. Chem.*, **29**, 1456 (1957).

(14) J. W. Knapczyk and W. E. McEwen, *J. Amer. Chem. Soc.*, **91**, 145 (1963).

TABLE I

PRODUCTS FROM IRRADIATION OF PHENACYLSULFONIUM TETRAFLUOROBORATES

Salt	Solvent	Time, hr	Products (% yield)
$C_6H_5\overset{O}{\overset{\|}{C}}CH_2\overset{+}{S}(CH_3)_2$ **1**	CH_3OH	6.2	$C_6H_5COCH_3$ (82) **2**
1	$(CH_3)_3COH$	3	**2** (33), $C_6H_5\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}C_6H_5$ (16), $C_6H_5\overset{O}{\overset{\|}{C}}CH_2CH_2SCH_3$ (5) **3** **4**
1	CH_3CN	5	**2** (60), **3** (14%)
 **5**	CH_3OH	12.7	 (40) **6**
 **7**	CH_3OH	8	 (61) **8**
 **9**	CH_3OH	20	 (79) **10**
$PhC(=O)CH_2\overset{+}{S}(n\text{-butyl})_2$ **11**	CH_3OH	4.5	**2** (48), $(n\text{-butyl})_2S$ (29) **12**
11	H_2O	2	**2** (16), **3** (14), **12** (29)

which would couple with the phenacyl radical to form the minor product **4**. The dimethyl sulfide isolated from photolysis of dimethylphenacylsulfonium bromide[3] and the di-*n*-butyl sulfide from **11** probably do not arise from hydrogen atom abstraction from water or methanol by the α-thioalkyl radical since such radicals are more stable than their oxygen analogs.[5a,15] A more reasonable explanation for formation of the dialkyl sulfide would be abstraction of a hydrogen atom by the dialkylsulfinium ion followed by loss of a proton.

The photolysis of benzylsulfonium tetrafluoroborates in methanol gives solvolytic products and radical products in line with conclusions drawn in previous photochemical studies of benzyl derivatives.[16] The sulfonium tetrafluoroborates studied are listed in Table II. Photolysis of **13** in methanol gives the solvolytic product **14** and the radical coupling product **15**. No toluene is observed as a radical abstraction product; benzyl radicals are known to prefer to couple rather than abstract hydrogen atoms.[17] Product **14** was found to photolyze slowly, but this did not account for the observed products **16–18** which undoubtedly arise from secondary reactions of **14**. It has been shown that a variety of radical initiators will abstract a hydrogen atom from the benzylic carbon of **14** to form an intermediate radical which fragments to **16**, or dimerizes to **18**.[18] Monomethyl ether **17** undoubtedly arose from coupling of the intermediate radical from **14** with the benzyl radical. Photolysis of **13** in *t*-butyl alcohol gave only **19** and **15**. No secondary products are formed owing to the steric inhibition to benzylic hydrogen atom abstraction by the *t*-butyl group of **19**.

The dibenzylmethylsulfonium salt, **22**, on irradiation gave a product mixture similar to that of **13**, except in this case the sulfur-containing product **23** was also isolated. Photolysis of **23** in methanol for 2 hr (80% reaction) gave **15** in 19% yield. Consequently, some of **15** formed during the photolysis of **22** may arise as a secondary product from **23**.

In view of Zimmerman's conclusions[16] on the enhancing effect of *m*-methoxy substitution on the photochemical solvolysis of benzylic systems, salt **24** was irradiated. The enhanced rate of reaction of **24** *vs.* that of **13** probably reflects only the more intense absorption of **24**. A longer irradiation for **24** rapidly decreased the yield of **25** and several unidentified secondary products appeared. Although the ratio of heterolytic/homolytic cleavage products would appear to decrease from **13** to **24**, the extent of secondary reactions that may be leading to polymer formation can not be determined and no conclusions can be drawn concerning the adequacy of Zimmerman's theoretical model. The formation of **28** from **24** probably involves coupling of the *p*-methoxybenzyl radical with the α-thioalkyl radical, $\cdot CH_2SCH_3$, derived from homolytic cleavage as suggested above.

Irradiation of salts **29** and **32** in methanol gave similar results. The major product from **29** is the photochemical solvolysis product **30**. The formation of **31** is explained in terms of a secondary photochemical reaction of **30** analogous to the photolysis of benzyl methyl sulfide described above except that the product is that resulting from hydrogen atom abstraction rather than radical coupling. Irradiation of **32** gives the solvolytic product **33** and the secondary product **34**. It is interesting to note that **33** preferentially cleaves to the substituted 2-phenylethyl radical and the thiyl radical

(15) S.-O. Lawesson and C. Berglund, *Acta Chem. Scand.*, **15**, 36 (1961).

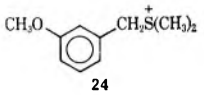
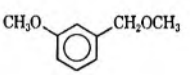
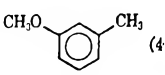
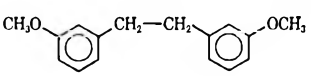
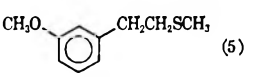
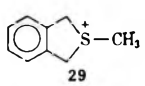
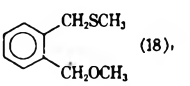
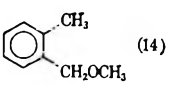
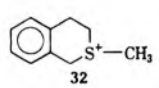
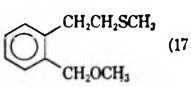
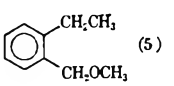
(16) H. E. Zimmerman and V. R. Sandel, *J. Amer. Chem. Soc.*, **85**, 915 (1963).

(17) W. A. Waters in "Vistas in Free Radical Chemistry," W. A. Waters, Ed., Pergamon Press, New York, N. Y., 1959, p 151.

(18) R. E. Lovins, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **30**, 4150 (1965).

TABLE II

PRODUCTS FROM IRRADIATION OF BENZYLSULFONIUM TETRAFLUOROBORATES

Salt	Solvent	Time, hr	Products (% yield)
$PhCH_2\overset{+}{S}(CH_3)_2$ **13**	CH_3OH	3.5	$PhCH_2OCH_3$ (25), **14**; $PhCH_2CH_2Ph$ (3), **15**; PhCHO (9), **16**; $PhCH(OCH_3)CH_2Ph$ (8), **17**; $PhCH(OCH_3)CH(OCH_3)Ph$ (7), **18**
13	$(CH_3)_3COH$	2.3	$PhCH_2OC(CH_3)_3$ (33), **19**; **15** (4)
13	CH_3CN	24	$PhCH_2NHC(=O)CH_3$ (70), **20**; $PhCH_2$–C$_6$H$_4$–CH_3 (7), **21**
$(PhCH_2)_2\overset{+}{S}CH_3$ **22**	CH_3OH	1.2	**14** (23), **15** (8), **16** (5), **17** (7), **18** (4), $PhCH_2SCH_3$ (26), **23**
 **24**	CH_3OH	0.25	 (53), **25**;  (4), **26**;  (8), **27**;  (5), **28**
 **29**	CH_3OH	2.5	 (18), **30**;  (14), **31**
 **32**	CH_3OH	3	 (17), **33**;  (5), **34**

rather than to the substituted benzyl radical and the α-thioalkyl radical. That **34** is formed from **33** was established by irradiation of **33** in methanol which gave **34** as the only nonpolymeric product.

Although poor leaving groups deter excited-state solvolysis,[18] the photolysis of **13** in acetonitrile suggests that excited-state solvolysis occurs in solvents of low nucleophilicity. Amide **20** must result from hydrolysis of the nitrilium salt,[19] $PhCH_2N^+{\equiv}CCH_3$, during the work-up procedure. Since radicals add to the carbon atom of nitriles,[20] **20** must arise from heterolytic cleavage rather than homolytic cleavage. The hydrocarbon **21**, however, may arise from the benzyl radical.

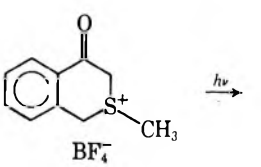
The above results clearly indicate that irradiation of phenacylsulfonium salts leads to homolytic cleavage whereas benzylsulfonium salts undergo predominantly heterolytic cleavage. Clearly, excitation of the benzylsulfonium salts leads to an initial π^*,π state. Whether the π^*,π state or the π^*,n state of the phenacylsulfonium salts is responsible for the observed reactions has not been determined. The π^*,n triplet state of phenacylsulfonium salts **1**, **5**, **7**, and **11** is of lower energy than the π^*,π triplet state, whereas the reverse is probably the case for **9**.[21] Nonetheless, the reaction course for **9** appears to be the same as the other phenacyl sulfonium salts studied.

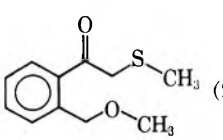
(19) H. Meerwein, *et al.*, *Chem. Ber.*, **89**, 209 (1956), report the isolation of a number of nitrilium salts, all of which rapidly hydrolyzed to amides.

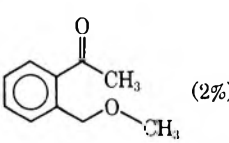
(20) J. R. Shelton and C. W. Uzelmeir, *J. Amer. Chem. Soc.*, **88**, 5222 (1966).

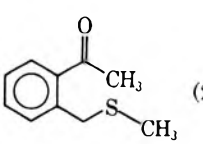
(21) By analogy to 2-acetonaphthalene: G. S. Hammond and P. A. Leermakers, *ibid.*, **84**, 207 (1962).

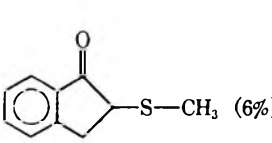
Irradiation of **35**, which is both a phenacyl and a benzylsulfonium salt, in methanol for 4.5 hr (84% reaction) led to products readily explained in terms of the

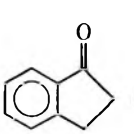

35

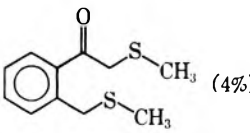
 (24%) **36**

 (2%) **37**

 (2%) **38**

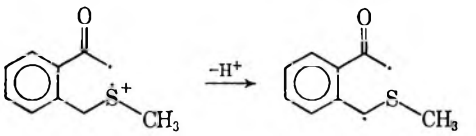
 (6%) **39**

 (3%) **40**

 (4%) **41**

above results. Solvolytic displacement at the benzylic carbon–sulfur bond leads to the major product **36**; product **37** is formed from **36** by a secondary homolytic

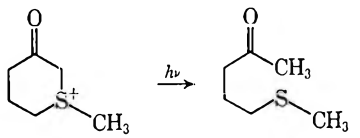
cleavage.[22] Homolytic cleavage, as observed for phenacyl sulfonium salts, leads to **42** which is converted to **38** by hydrogen atom abstraction and to **39** by loss of H^+ to **43** which ring closes. Indanone (**40**) is formed



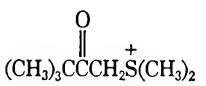
42 **43**

from **39** in an analogous fashion to the secondary photolysis of **36** to **37**. Several reasonable pathways explain the formation of **41**.

Irradiation of β-ketosulfonium salt **44** in methanol for 20 hr gave **45** in low yield (2%) as the sole nonpolymeric product. Tetrafluoroborate salt **46** gave no



44 **45**



46

monomeric products on irradiation in methanol for 38 hr (43% decomposition).

Experimental Section[23]

Photochemical Studies.—Photolyses were conducted in the Rayonet "Photochemical Reactor."[24] The materials photolyzed are listed in Table III. The irradiations were carried out in a Pyrex vessel with a 3000-Å source (source a) or in a quartz vessel with a 2537-Å source (source b). The reaction vessels were equipped with a magnetic stirring bar, a gas dispersion tube, and a reflux condenser. Tubes sealed with "no air" stoppers served as convenient reaction vessels for small quantities of material. Photochemical solvents were dried and distilled directly into the photolysis vessel under N_2. Methanol (Baker "Reagent") was dried by reaction with Mg turnings; *t*-butyl alcohol (Eastman Organic Chemicals) was distilled from $LiAlH_4$; acetonitrile (Eastman Organic Chemicals, "Spectrograde") was distilled from P_2O_5. The solutions were degassed prior to irradiation with a moderate stream of N_2 for at least 2 hr.

All photolyses were monitored by analysis (tlc or glpc) of samples withdrawn at convenient intervals of time. For photolyses monitored by glpc, a known amount of hydrocarbon standard[25] was added before irradiation.

TABLE III
PHOTOCHEMICAL STUDIES

Compound irradiated (wt, g)	Solvent (vol, ml)	Source	Time, hr	Amount of compound recovered
$PhCOCH_2\overset{+}{S}(CH_3)_2Br^-$ (1.222)	CH_3OH (450)	a	7.5	0
$PhCOCH_2Br$ (0.483)	CH_3OH (300)	a	3	<10
1 (0.515)	CH_3OH (350)	a	6.2	0
1 (0.186)	*t*-butyl alcohol (900)	a	3	0
2 (0.375)	CH_3CN (300)	a	5	0
5 (1.35)	CH_3OH (450)	a	12.7	0
7 (0.803)	CH_3OH (300)	a	8	0
$PhCOCH_2OCH_3$ (0.222)	CH_3OH (75)	a	2	0
9 (0.125)	CH_3OH (300)	a	20	0
11 (0.750)	CH_3OH (300)	a	4.5	0
11 (0.554)	H_2O (300)	a	2	0
$PhCOCH_2OH$ (0.080)	H_2O (25)	a	2	87
13 (0.612)	CH_3OH (500)	b	3.5	0
13 (0.187)	*t*-butyl alcohol (600)	b	2.3	0
13 (0.622)	CH_3CN (500)	b	24	0
$PhCH_2OCH_3$ (0.196)	CH_3OH (60)	b	4	58
22 (1.12)	CH_3OH (500)	b	1.2	0
24 (0.583)	CH_3OH (500)	b	0.25	0
29 (1.058)	CH_3OH (450)	b	2.5	12
32 (1.97)	CH_3OH (500)	b	3	34
32 (0.715)	CH_3CN (300)	a	4	0
33 (0.010)	CH_3OH (1)	b	0.75	20
$PhCH_2SCH_3$ (0.157)	CH_3OH (60)	b	2	20
35 (1.93)	CH_3OH (450)	a	4.5	16
44 (0.475)	CH_3OH (500)	b	20	0
46 (1.060)	CH_3OH (450)	b	38	57

After irradiation of the salts, the solution was concentrated to *ca.* half its original volume, an equal volume of $CHCl_3$ or ether was added and the solution was concentrated. If a solid separated, the solution was cooled and the solid was recovered by filtration. The process was repeated until no more solid was recovered. In all cases in which pure material was obtained the recovered solid was unreacted starting material. If a weighed quantity of standard had not been added previously, it was added at this point. The solution was washed with H_2O, dilute $NaHCO_3$, saturated NaCl, and dried. The residue was analyzed by glpc. All products listed were identified by collection from glpc and comparison with an authentic sample. Yields were determined

(22) Acyclic β-keto sulfides have been shown to cleave in this fashion: J. R. Collier and J. Hill, *Chem. Commun.*, 700 (1968), and references cited therein.

(23) Infrared spectra were taken on a Perkin-Elmer Model 237 or 337 spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 spectrophotometer. The nmr spectra were taken on a Varian A-60 or T-60 spectrometer and are reported in parts per million downfield from TMS at 0.00. Mass spectra were run on a Perkin-Elmer Hitachi RMU-6D spectrometer with an ionizing potential of 80 eV. Melting points were taken on a Thomas–Hoover "Uni Melt" and are corrected. Boiling points are uncorrected. Gas chromatographic analyses and isolations were performed on an F & M Model 810 research chromatograph (thermal conductivity detector) utilizing 4 ft × 1/4 in. columns packed with either 15% SE-30 on neutral 60–80 mesh Chromosorb P or 15% Carbowax 20M on the same support. In general reactions were conducted under an atmosphere of N_2 and $MgSO_4$ was used to dry organic extracts. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, or Galbraith Laboratories, Knoxville, Tenn.

(24) Model RPR100 (Southern New England Ultraviolet Co., Middletown, Conn.): reactor barrel, 10 in. (diameter) by 15 in. (depth) with 16 lamps in a circular bank.

(25) *n*-Dodecane (Matheson Co.), *n*-tetradecane and *n*-octadecane (Columbia Organic Chemicals Co.), or *n*-heptadecane (Aldrich Chemical Co.).

from calibrated glpc curves. Table III lists the pertinent data that was not adequately described in Tables I or II or elsewhere in the discussion section. The products listed in Tables I and II were not formed when the salts were dissolved in methanol and were allowed to stand in the absence of light.

Preparation of Tetrafluoroborate Salts. Method A.—A solution of 10–25 mmol of $AgBF_4$ in 25–30 ml of ethanol was added dropwise with stirring to a solution containing an equivalent amount of sulfonium bromide in 300–350 ml of ethanol and the mixture was stirred for 1 hr. The mixture was filtered, the solid was washed with hot methanol, and the filtrate and washings were combined and concentrated to a residue that was recrystallized from ethanol.

Method B.—The preparation of sulfonium tetrafluoroborates from the corresponding sulfides involved preparation of a solution of 5–20 g of trimethyloxonium tetrafluoroborate[26] in 20–100 ml of nitromethane in a flask sealed with a "no air" stopper. The required sulfide, neat or in a small quantity of solvent, was added to the well-stirred solution. In some cases a vigorous exothermic reaction ensued which was moderated by occasional immersion in an ice bath. The solution was stirred 30–60 min at room temperature and was allowed to stand in the refrigerator overnight. If crystallization occurred, the product was claimed by filtration; if it did not, the solvent was removed and a small quantity of ether was added to the residue, which then usually crystallized. The crude salt was recrystallized from an appropriate solvent.

Dimethylphenacylsulfonium Tetrafluoroborate (1).—Salt **1** was prepared in 57% yield from dimethylphenacylsulfonium bromide[27] by method A: mp 168.5–170°; uv max (CH_3OH) 249 nm (ϵ 12,700) and 285 (2240); nmr (acetone-d_6) δ 3.18 (s, 6), 5.55 (s, 2), 7.55–7.87 (m, 3) and 8.01–8.21 (m, 2).

Anal. Calcd for $C_{10}H_{13}BF_4OS$: C, 44.79; H, 4.89; S, 11.96. Found: C, 44.85; H, 4.99; S, 12.18.

1,2-Dibenzoylethane (3) was prepared from benzene and succinoylchloride:[28] mp 144–146° (lit.[28] mp 144–145°).

3-(Methylthio)propiophenone (4) was prepared in 74% yield from 3-chloropropiophenone and $NaSCH_3$: mp 35–37° (lit.[29] mp 35–36°).

1-Oxo-1,2,3,4-tetrahydronaphthalenyldimethylsulfonium Tetrafluoroborate (5).—2-Bromo-1-tetralone[30] (45.5 g, 0.202 mol) was added to a cold (0°) solution of 0.244 mol of $NaSCH_3$ in 150 ml of absolute ethanol. The solution was stirred overnight at room temperature, concentrated, and poured into water. The mixture was extracted with ether, and the combined extracts were washed with water, saturated NaCl solution, and dried. The crude residue was distilled to give 6.8 g (23%) of 1-tetralone[31] (**6**) and 17.8 g (46%) of 2-methylthio-1-tetralone as a pale yellow oil: bp 88–90° (0.09 mm); ir (CCl_4) 1682 cm^{-1}; uv max (CH_3OH) 248 nm (ϵ 10,000), 279 (2420) and 327 (630); nmr (CCl_4) δ 2.05 (s, 3), 2.05–3.45 (m, 5), 6.88–7.55 (m, 3), and 7.77–8.12 (m, 1); mass spectrum *m/e* (rel intensity) 192 (19), 146 (100), 145 (42), 118 (33), 115 (39) and 90 (30).

Anal. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.29; S, 16.68. Found: C, 68.46; H, 6.29; S, 16.67.

2-Methylthio-1-tetralone was converted in 71% yield to **5** by method B: mp 114–116°; ir (KBr) 1682 and 1125–1035 cm^{-1}; uv max (CH_3OH) 254 nm (ϵ 12,500) and 303 (2610); nmr (dimethyl sulfoxide-d_6) δ 2.33–3.44 (m, 4), 2.83 (s, 3) 2.95 (s, 3), 5.10 (d of d, 1, J = 12 and 5.5 Hz), and 7.13–7.97 (m, 4).

Anal. Calcd for $C_{12}H_{15}BF_4OS$: C, 49.00; H, 5.14; S, 10.90. Found: C, 49.14; H, 5.17; S, 11.18.

***m*-Methoxyphenacyldimethylsulfonium Tetrafluoroborate (7).**—Solid 2-bromo-*m*-methoxyacetophenone (25.0 g, 0.109 mol) (Aldrich Chemical Co.) was added to a cold (0°) solution of $NaSCH_3$ in 150 ml of ethanol and the solution was stirred for 5 hr at room temperature. Water was added and the solution was concentrated and poured into ether. The aqueous layer was removed and extracted with ether. The combined ether extracts were washed with water, saturated NaCl solution, and dried. The crude residue was distilled to give 2.33 g (14%) of *m*-methoxyacetophenone (**8**), bp 57–59° (0.08 mm) [lit.[32] bp 125° (14 mm)], and 14.1 g (66%) of 2-methylthio-*m*-methoxyacetophenone: bp 93–95° (0.08 mm); ir (CCl_4) 1677 cm^{-1}; uv max (CH_3OH) 250 nm (ϵ 6580), 307 (2450) and 345 (495); nmr (CCl_4) δ 2.00 (s, 3) 3.57 (s, 2), 3.67 (s, 3), and 6.77–7.50 (m, 4); mass spectrum *m/e* (rel intensity) 196 (18), 150 (15), 135 (100), 107 (33), 94 (18), 92 (21), 79 (11), 77 (32), 64 (18), 63 (15), 61 (17), 50 (10), 47 (14), 46 (11), 45 (20), and 43 (16).

Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.16; S, 16.34. Found: C, 61.31; H, 6.31; S, 16.49.

2-Methylthio-*m*-methoxyacetophenone was converted in 79% yield to **7** by method B: mp 163–165°; ir (KBr) 1678 cm^{-1}; uv max (CH_3OH) 220 nm (ϵ 19,500), 256 (9090), and 312 (3510); nmr (dimethyl sulfoxide-d_6) δ 2.95 (s, 6) 3.82 (s, 3), 5.37 (s, 2) and 7.13–7.67 (m, 4).

Anal. Calcd for $C_{11}H_{15}BF_4O_2S$: C, 44.31; H, 5.07; S, 10.76. Found: C, 44.51; H, 5.11; S, 10.95.

(2-Naphthoyl)methyldimethylsulfonium Tetrafluoroborate (9).—A solution of 8.6 g (0.034 mol) of 2-bromoacetonaphthalene (Aldrich Chemical Co.) in 50 ml of acetone containing 2 ml of water was cooled to 0° and treated with 5 ml of dimethyl sulfide. The solution was stirred 10 min at 0°, warmed to room temperature, and stirred an additional hour. The white precipitate was filtered and recrystallized from ethanol to give 5.10 g (48%) of the sulfonium bromide: mp 133–135° dec; ir (KBr) 1678 cm^{-1}. The bromide was converted in 36% yield to the tetrafluoroborate by method A; mp 157.5–159.5°; ir (KBr) 1672 and 1125–1035 cm^{-1}; uv max (CH_3OH) 233 nm (ϵ 31,200), 244 (32,100), 253 (36,400), 287 (11,620), 296 (11,860), 317 (4230) (sh), and 332 (3090); nmr (dimethyl sulfoxide-d_6) δ 3.03 (s, 6), 5.53 (s, 2), 7.47–8.27 (m, 6) and 8.73 (s, 1).

Anal. Calcd for $C_{14}H_{15}BF_4OS$: C, 52.85; H, 4.75; S, 10.08. Found: C, 52.65; H, 4.83; S, 10.33.

Di-*n*-butylphenacylsulfonium Tetrafluoroborate (11).—Salt **11** was prepared from phenacyl bromide and di-*n*-butyl sulfide followed by conversion to the tetrafluoroborate salt by method A using the overall procedure described for the preparation of **1**. The bromide salt was obtained in 31% yield: mp 90–92° (lit.[33] mp 88–89°). The tetrafluoroborate salt **11** was obtained in 80% yield: mp 81.5–83°; ir (KBr) 1688 and 1120–1020 cm^{-1}; uv max (CH_3OH) 247 nm (ϵ 11,400) and 288 (4300); nmr (dimethyl sulfoxide-d_6) δ 0.73–2.13 (m, 14), 3.17–3.60 (m, 4), 5.40 (s, 2), and 7.50–8.23 (m, 5).

Anal. Calcd for $C_{16}H_{25}BF_4OS$: C, 54.55; H, 7.15; S, 9.10. Found: C, 54.34; H, 7.08; S, 9.36.

Benzyldimethylsulfonium tetrafluoroborate (13) was prepared in 71% yield from benzyl methyl sulfide by method B: mp 101–103° (ethanol); ir (KBr) 1125–1030 cm^{-1}; uv max (CH_3OH) 254 nm (ϵ 221), 260 (302), 265 (314), and 271 (232); nmr (acetone-d_6) δ 2.90 (s, 6), 4.73 (s, 2) and 7.30–7.70 (broad s, 5).

Anal. Calcd for $C_9H_{13}BF_4S$: C, 45.02; H, 5.46; S, 13.36. Found: C, 45.12; H, 5.47; S, 13.52.

1,2-Diphenyl-1-methoxyethane (17).—1,2-Diphenylethanol (5.00 g, 0.252 mol; Eastman Organic Chemicals) was added all at once to a suspension of 1.78 g of a 61% mineral oil dispersion of NaH (0.0453 mol) in 50 ml of ether. The mixture was stirred at reflux for 4 hr, cooled to 0°, and excess CH_3I (5 ml) was added. The suspension was stirred at room temperature overnight and treated with water, and the layers were separated. The aqueous layer was extracted with ether and the combined ether extracts were washed with water and saturated NaCl solution and were dried. The ether was removed under reduced pressure, and the mixture partially crystallized when a few milliliters of hexane were added. The crystalline material was filtered from the solution and recrystallized from hexane giving 1.40 g of starting material. The filtrate was passed over 150 g of alumina (Woelm, activity I). The desired product (**17**) was eluted with hexane, following a forerun of mineral oil, and was short-path distilled giving 1.84 g (45%) of **17**. The spectra data of this product were identical with that previously reported.[34]

***meso*-1,2-Dimethoxy-1,2-diphenylethane (18)** was prepared in 78% yield from *meso*-1,2-diphenyl-1,2-ethanediol[35] by the same procedure used to prepare **17** except that tetrahydrofuran was used in place of ether as the solvent: mp 141–143° (lit.[36] mp 140–142°).

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Benzyl *t*-butyl ether (19) was prepared in 59% yield as previously described:[37] bp 85–86° (9 mm) [lit.[37] bp 206–208° and 38–41° (0.5 mm)[38]].

N-Benzylacetamide (20) was obtained in 59% yield from benzylamine and acetyl chloride: mp 61–63° (lit.[39] mp 60–61°).

Dibenzylmethylsulfonium tetrafluoroborate (22) was prepared in 56% yield from dibenzyl sulfide (Eastman Organic Chemicals) by method B: mp 115–116.5° (from acetone–ether); ir (KBr) 1125–1140 cm^{-1}; uv max (CH_3OH) 253.5 nm (ϵ 538), 260 (655), 265 (631), and 271 (430); nmr (acetone-d_6) δ 2.82 (s, 3), 4.87 (AB pattern, 4, J = 18 Hz) and 7.18–7.72 (m, 10).

Anal. Calcd for $C_{15}H_{17}BF_4S$: C, 56.98; H, 5.42; S, 10.14. Found: C, 56.99; H, 5.35; S, 10.19.

***m*-Methoxybenzyldimethylsulfonium Tetrafluorcborate** (24).—*m*-Methoxybenzyl bromide[40] was converted in 79% yield to *m*-methcxybenzyl methyl sulfide by the same procedure described for the preparation of 2-methylthio-1-tetralone: bp 62–63° (0.08 mm); ir (CCl_4) 1268 cm^{-1}; uv max (CH_3OH) 275 nm (ϵ 2230) and 282.5 (2030); nmr (CCl_4) δ 1.85 (s, 3), 3.50 (s, 2), 3.62 (s, 3), and 6.46–7.32 (m, 4); mass spectrum *m/e* (rel intensity) 168 (17), 122 (21), 121 (100), 91 (53), 78 (57), 77 (41), 65 (26), 63 (23), 52 (24), 51 (37), and 45 (27).

Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19; S, 19.06. Found: C, 64.43; H, 7.17, S, 19.30.

m-Methoxybenzyl methyl sulfide was converted in 53% yield to **24** by method B: mp 59–61° (from ethanol); ir (KBr) 1175–950 cm^{-1}; uv max (CH_3OH) 278 nm (ϵ 3110) and 283 (3020); nmr (acetone-d_6) δ 2.97 (s, 6), 3.82 (s, 3), 4.72 (s, 2), and 6.85–7.53 (m, 4).

Anal. Calcd for $C_{10}H_{15}BF_4OS$: C, 44.46; H, 5.60; S, 11.87. Found: C, 44.30; H, 5.46; S, 12.06.

***m*-Methoxybenzyl methyl ether** (25) was prepared in 55% yield from *m*-methoxybenzyl bromide[40] and $NaSCH_3$ in methanol: bp 50–52° (0.38 mm) [lit.[41] bp 52–53° (0.3 mm)].

1,2-Bis(*m*-methoxyphenyl)ethane (27) was prepared in 60% yield as previously reported:[42] bp 142–145° (0.3 mm) [lit.[43] bp 203–205° (10 mm)].

2-Methylthio-*m*-methoxyethylbenzene (28).—A mixture of 9.03 g (0.0461 mol) of 2-methylthio-*m*-methoxyacetophenone, 65 ml of diethylene glycol, 8 ml of hydrazine hydrate (99–100%), and 2.50 g of KOH was heated slowly to 110–120°, maintained at that temperature for 1 hr, and then heated at 170–190° for 1 hr. The solution was cooled, treated with water, and extracted with several portions of ether. The combined ether solutions were washed with saturated NaCl solution and dried. The crude mixture was distilled to give 2.6 g of a low-boiling [bp 28° (0.02 mm)] forerun consisting of a mixture and the desired product **28** (1.01 g) in 12% yield: bp 64–65° (0.02 mm); ir (CCl_4) 2915, 1601, 1490, 1262, 1153, and 1053–1045 cm^{-1}; uv max (CH_3OH) 273 nm (ϵ 1870) and 278 (1660); nmr (CCl_4) δ 2.00 (s, 3), 2.37–2.90 (m, 4), 3.67 (s, 3), and 6.43–7.20 (m, 4); mass spectrum *m/e* (rel intensity) 182 (40), 134 (37), 121 (44), 91 (31), and 61 (100).

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74; S, 17.59. Found: C, 66.06; H, 7.69; S, 17.80.

2-Methyl-1,3-dihydroisothianaphthenium tetrafluoroborate (29) was prepared in 68% yield from 1,3-dihydroisothionaphthene:[44] mp 146.5–148° (from ethanol); ir (KBr) 1142–1033 cm^{-1}; uv max (CH_3OH) 252 nm (ϵ 164), 257.5 (228), 263.5 (298), and 271 (271); nmr (acetone-d_6) δ 2.92 (s, 3), 4.95 (AB pattern, 4, J = 16.5 Hz) and 7.25–7.75 (m, 4).

Anal. Calcd for $C_9H_{11}BF_4S$: C, 45.40; H, 4.66; S, 13.47. Found: C, 45.48; H, 4.82; S, 13.68.

***o*-(Methylthio)methylbenzyl Methyl Ether** (30).—*o*-(Methylthio)methylbenzoic acid (6.0 g, 0.033 mol) was esterified with ethanol and H_2SO_4 by standard procedures to give in 89% yield ethyl *o*-(methylthio)methylbenzoate: bp 82.5–85° (0.13 mm); ir (CCl_4) 1725 cm^{-1} uv max (C_2H_5OH) 227 nm (ϵ 10,250) and 282 (1350); nmr (CCl_4) δ 1.28 (t, 3, J = 7 Hz) 1.83 (s, 3) 4.01 (s, 2) 4.25 (q, 2, J = 7 Hz), 7.00–7.33 (m, 3) and 7.70–7.95 (m, 1); mass spectrum *m/e* (rel intensity) 210 (39), 165 (34), 164 (56), 149 (100), 135 (61), 133 (67), 118 (23), 90 (19), and 77 (20).

Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.82; H, 6.71; S, 15.25. Found: C, 62.80; H, 6.68; S, 15.10.

To 720 mg (19.0 mmol) of $LiAlH_4$ in 10 ml of ether at 0° was added dropwise a solution of 3.77 g (18.0 mmol) of ethyl *o*-(methylthio)methylbenzoate in 10 ml of ether. The mixture was stirred for 3 hr at room temperature and was then treated successfully with 1 ml of ethyl acetate, 2 ml of water, and 10 ml of 5% HCl. The aqueous layer was extracted twice with ether and the combined ether layers were washed with saturated solutions of $NaHCO_3$ and NaCl and then dried. The crude product was chromatographed on 25 g of silicic acid with $CHCl_3$. The first fractions contained some unreacted ester. The later fractions were combined and distilled to give 1.73 g (57%) of *o*-(methylthio)methylbenzyl alcohol: bp 84–87° (0.1 mm); ir (CCl_4) 3605, 3460 (broad), and 1010 cm^{-1}; uv max (CH_3OH) 240 nm (ϵ 953) (sh), 261 (479), 267 (331) (sh), 272 (226) (sh) and 290 (16); nmr ($CDCl_3$) δ 2.80 (s, 3), 3.57 (s, 2), 4.25–4.67 (broad s, 1; disappears on addition of D_2O), 4.56 (s, 2) and 7.00–7.35 (m, 4); mass spectrum *m/e* (rel intensity) 168 (5), 167 (4), 135 (24), 121 (18), 120 (100), 119 (47), 91 (41), and 77 (26).

Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19; S, 19.06. Found: C, 64.06; H, 7.08; m, 19.30.

To a suspension of 850 mg of 61% mineral oil dispersion of NaH (21.6 mmol) in 50 ml of ether was added 1.26 g (7.49 mmol) of *o*-(methylthio)methylbenzyl alcohol. The mixture was stirred for 6 hr and 0.55 ml of CH_3I was added to the thick paste. Stirring was continued overnight. Ethanol and then water were added cautiously to the mixture. The aqueous layer was extracted with ether and the combined ether layers were dried. The crude product was chromatographed over 10 g of silicic acid. The mineral oil was eluted with hexane, the desired product **30** with 10% ether–hexane, and starting material with 1% methanol–ether. Fractions containing **30** were short-path distilled to give 81 mg (6%) of pure **30**: ir (CCl_4) 1102 cm^{-1}; uv max (CH_3OH) 242 nm (ϵ 947) (sh), 262 (510) (sh), 274 (226) (sh) and 289 (33); nmr (CCl_4) δ 1.73 (s, 3), 3.13 (s, 3), 3.17 (s, 2), 4.33 (s, 2), and 7.00 (m, 4); mass spectrum *m/e* (rel intensity) 135 (42), 134 (100), 119 (40), 105 (28), 104 (17), 91 (27), and 77 (9).

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74; S, 17.59. Found: C, 66.04; H, 7.84; S, 17.74.

***o*-Methylbenzyl methyl ether** (31) was prepared in 58% yield as previously described: bp 86–87° (20 mm) [lit.[45] bp 97° (32 mm)]; ir (CCl_4) 1098 cm^{-1}; nmr (neat) 2.14 (s, 3), 3.17 (s, 3), 4.21 (s, 2), and 6.90–7.37 (m, 4); mass spectrum *m/e* (rel intensity) 136 (12), 135 (10), 121 (22), 105 (48), 104 (100), 91 (16), and 77 (15).

2-Methylisothiochromanium tetrafluoroborate (32) was prepared in 66% yield from isothiochromate[46] by method B: mp 94–96° (from ethanol); ir (KBr) 1125–1030 cm^{-1}; uv max (CH_3OH) 262 nm (ϵ 245), 265 (240) (sh), and 271 (192); nmr (dimethyl sulfoxide-d_6) δ 2.53 (s, 3), 2.70–3.93 (m, 4), 4.47 (AB pattern, 2, J = 15 Hz), and 7.40 (s, 4).

Anal. Calcd for $C_{10}H_{13}BF_4S$: C, 47.64; H, 5.20; S, 12.72. Found: C, 47.82; H, 5.35; S, 12.82.

***o*-(2-Methylthio)ethylbenzyl Methyl Ether** (33).—A solution of 2.60 g (0.0103 mol) of **32** and 8.0 g (0.059 mol) of $NaOAc \cdot 3H_2O$ in 50 ml of water was refluxed for 2.5 days. The pH of the solution was maintained between 6–7 by the addition of dilute KOH solution as necessary. An oil gradually separated. The mixture was treated with methanol and dilute KOH solution, refluxed for 1 hr, cooled, and extracted with ether. The combined ether extracts were washed with water and saturated NaCl solution and dried. The crude residue was chromatographed over 20 g of alumina (Woelm, activity I). Elution with 10% ether–hexane gave 63 mg of by-products. Elution with 1% methanol–ether gave 166 mg of *o*-(2-methylthio)ethylbenzyl alcohol: ir (CCl_4) 3610, 3510 (broad) and 1003 cm^{-1}. The alcohol (126 mg, 0.69 mol) was added to a suspension of 163 mg of a 61% mineral oil dispersion of NaH (4.1 mmol) in 10 ml of tetrahydrofuran. The mixture was refluxed for 1 hr, cooled, treated with 50 μl of CH_3I, refluxed for 1 hr and cooled. Water was added cautiously and

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the aqueous layer was extracted with ether. The combined ether layers were washed with saturated NaCl solution and dried. The major component (**33**) was collected by glpc: ir (CCl_4) 1103 cm^{-1}; uv max (CH_3OH) 260 nm (ϵ 320), 266 (306) (sh), and 271 (246); nmr (CCl_4) δ 2.00 (s, 3), 2.37–3.03 (m, 4), 3.23 (s, 3), 4.33 (s, 2), and 7.07 (s, 4); mass spectrum *m/e* (rel intensity) 196 (44), 149 (15), 148 (20), 147 (25), 121 (39), 117 (97), 116 (100), 115 (31), 105 (48), 104 (18), 91 (27), 77 (15), 61 (50), and 45 (18).

Anal. Calcd for $C_{11}H_{16}OS$: C, 67.30; H, 8.21; S, 16.34. Found: C, 67.35; H, 8.14; S, 16.24.

***o*-Ethylbenzyl Methyl Ether (34).**—A mixture of 2.34 g (0.014 mol) of **37**, 3 ml of hydrazine hydrate (99–100%), 1.0 g of KOH, and 50 ml of diethylene glycol were heated at 110–120° for 1 hr and then warmed to 180–190° and maintained at that temperature for 2 hr. The distillate was collected in a Dean–Stark water separator. The cooled mixture was poured into water and extracted with ether. The combined ether layers were washed with saturated NaCl solution and dried. The crude product was distilled to give 1.35 g (63%) of **34**: bp 24–25° (0.03 mm); ir (CCl_4) 1098 cm^{-1}; uv max (CH_3OH) 263 nm (ϵ 238) and 271 (204); nmr (CCl_4) δ 1.13 (t, 3, J = 7.5 Hz), 2.60 (q, 2, J = 7.5 Hz), 3.20 (s, 3), 4.33 (s, 2), and 6.83–7.37 (m, 4); mass spectrum *m/e* (rel intensity) 150 (1), 149 (2), 121 (16), 119 (23), 118 (100), 117 (43), 91 (18), and 77 (12).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.42. Found: C, 80.16; H, 9.62.

2-Methyl-4-oxoisothiochromanium tetrafluoroborate (35) was prepared in 71% yield from isothiochroman-4-one[47] by method B: mp 158.5–59.5° (from 9:1 ethanol–methanol); ir (KBr) 1690 and 1025–1125 cm^{-1}; uv max (CH_3OH) 254 nm (ϵ 6760), 294 (1950), and 315 (1270) (sh); nmr (dimethyl sulfoxide-d_6) δ 2.83 (s, 3), 4.48 (AB pattern, 2, J = 15 Hz), 4.85 (AB pattern, 2, J = 15 Hz) and 7.37–8.12 (m, 4).

Anal. Calcd for $C_{10}H_{11}BF_4OS$: C, 45.14; H, 4.17; S, 12.05. Found: C, 45.10; H, 4.08; S, 12.26.

***o*-Methoxymethyl-2-methylthioacetophenone (36).**—Bromine (1.89 g, 0.0118 mol) in 10 ml of CS_2 was added dropwise over a 30-min period to a cold (−5°) solution of 1.22 g (0.0744 mol) of **37** in 10 ml of CS_2. The solution was stirred for 10 min, and water and ether were added. The organic layer was removed and washed with water, dilute $NaHSO_3$ solution, dilute $NaHCO_3$ solution, and saturated NaCl solution. The solvent was removed at 0° and the residue was dissolved in 20 ml of absolute ethanol. The solution was added all at once to a cold (0°) solution of 0.012 mol of $NaSCH_3$ in 15 ml of ethanol. The solution was warmed to room temperature, stirred for 30 min, and treated with water. The solution was extracted with several portions of ether, and the combined ether extracts were washed several times with water and saturated NaCl solution and dried. The residue was chromatographed over 100 g of silicic acid. The product, eluted with 5% ether in hexane, was short-path distilled to give 793 mg (51%) of **36**: ir (CCl_4) 1671 cm^{-1}; uv max (CH_3OH) 243 nm (ϵ 7780), 278 (2130) and 320 (802) (sh); nmr (CCl_4) δ 2.08 (s, 3), 3.40 (s, 3), 3.58 (s, 2), 4.68 (s, 2), and 7.08–7.82 (m, 4); mass spectrum *m/e* (rel intensity) 210 (5), 119 (32), 105 (14), 103 (12), 91 (60), 90 (14), 89 (15), 77 (26), 65 (15), 63 (13), 61 (12), 51 (18), and 45 (16).

Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.82; H, 6.71; S, 15.25. Found: C, 63.00; H, 6.82; S, 15.37.

***o*-(Methoxy)methylacetophenone (37).**—The procedures of Ramsden, *et al.*,[48] and Newman and Booth[49] were adapted to reaction of the Grignard reagent of *o*-chlorobenzyl methyl ether[50] with acetic anhydride to produce **37** in 48% yield: bp 46–47° (0.06 mm); ir (CCl_4) 1685 cm^{-1}; uv max (C_2H_5OH) 242 nm (ϵ 8290) and 284 (1130); nmr (neat) δ 2.43 (s, 3), 3.33 (s, 3), 4.73 (s, 2), and 7.10–7.80 (m, 4); mass spectrum *m/e* (rel intensity) 164 (47), 149 (68), 131 (100), 103 (48), 91 (37), 77 (32), and 43 (44).

Anal. Calcd for $C_9H_{12}O_2$: C, 73.14; H, 7.36. Found: C, 72.92; H, 7.43.

***o*-(Methylthio)methylacetophenone (38).**—Authentic **38** was prepared by Dr. R. E. Kohrman in these laboratories.[51]

2-Methylthioindan-1-one (39).—The ethylene ketal of 2-bromoindan-1-one[52] (7.09 g, 0.0276 mol) was added all at once to a solution of 0.052 mol of $NaSCH_3$ in 50 ml of ethanol; the mixture was stirred overnight at room temperature and was then refluxed for 1 hr. Water (20 ml) and concentrated HCl (10 ml) were added, and the solution was refluxed for 3 hr, cooled, and poured into ether. The ether layer was washed several times with water, dilute $NaHCO_3$ solution, and saturated NaCl solution and was dried. Glpc analysis showed the presence of 1-indanone and two major components that were collected from SE-30. The lower-boiling component was not investigated. The other component, **39**, was purified by glpc: ir (CCl_4) 1717 cm^{-1}; uv max (CH_3OH) 248 nm (ϵ 12,500), 290 (2480) and 345 (367); nmr (CCl_4) δ 2.16 (s, 3), 2.33–3.77 (m, 3), and 7.10–7.77 (m, 4); mass spectrum *m/e* (rel intensity) 178 (15), 135 (23), 134 (15), 133 (12), 132 (100), 131 (45), 103 (31), 102 (22), 91 (22), 89 (12), 77 (35), 76 (16), 75 (13), 74 (12), 63 (15), 51 (27), 50 (20), and ≤5 (15).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65. Found: C, 67.10; H, 5.87.

***o*-(Methylthio)methyl-2-methylthioacetophenone (41).**—Excess methanethiol (*ca.* 25 g) was condensed by means of a Dry Ice condenser in a flask containing 1.0 g (0.043 g-atom) of Na. One drop of methanol was added and the contents of the flask were stirred at 0° until no further reaction was evident (*ca.* 1 hr). Compound **35** (0.672 g, 2.52 mmol) was added to the gray suspension and the mixture was stirred for 30 min at 0°, refluxed for 30 min, and cooled to 0°. Cold ether (25 ml) was added, the mixture was allowed to warm to room temperature, and it was stirred overnight. Water (10 ml) was added and the ether solution was washed several times with water and saturated NaCl solution and dried. Compound **41** was collected from the crude product mixture by glpc and was short-path distilled: ir (CCl_4) 1680 cm^{-1}; uv max (CH_3OH) 241 nm (ϵ 7890), 275 (1900) and 320 (586) (sh); nmr (CCl_4) δ 1.93 (s, 3), 2.13 (s, 3), 3.57 (s, 2); 3.88 (s, 2), and 7.00–7.83 (m, 4); mass spectrum *m/e* (rel intensity) 226 (7), 179 (12), 166 (12), 165 (100), 131 (19), 119 (15), 118 (16), 91 (11), 90 (13), and 89 (10).

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.19; H, 6.12; S, 28.16.

1-Methyl-3-oxotetrahydrothiopyranium tetrafluoroborate (44) was prepared in 36% yield from tetrahydrothiopyran-3-one[53] by method B: mp 153.5–155.5° (from acetone–ether); ir (KBr) 1730 and 1125–1025 cm^{-1}; uv max (CH_3OH) 261 nm (31.6); nmr (acetone-d_6) δ 2.50–2.90 (m, 4), 3.11 (s, 3), 3.50–4.10 (m, 2), and 4.20 (AB pattern, 2, J = 15 Hz).

Anal. Calcd for $C_6H_{11}BF_4OS$: C, 33.05; H, 5.09; S, 14.71. Found: C, 32.81; H, 4.98; S, 14.96.

2-Thiaheptan-6-one (45) was prepared in 67% yield as previously described: bp 83–84° (8 mm) [lit.[54] bp 90–92° (18 mm)].

(2-Oxo-3,3-dimethyl)butyldimethylsulfonium tetrafluoroborate (46) was prepared in 81% yield from 5,5-dimethyl-2-thiahexan-4-one[55] by method B: mp 107.5–109° (from ethanol); ir (KBr) 1705 and 1125–1010 cm^{-1}; uv max (CH_3OH) 278 nm (49.4); nmr (dimethyl sulfoxide-d_6) δ 1.13 (s, 9), 2.83 (s, 6), and 4.92 (s, 2).

Anal. Calcd for $C_8H_{17}BF_4OS$: C, 38.72; H, 6.94; S, 12.93. Found: C, 38.59; H, 6.84; S, 13.15.

Registry No.—**1**, 24806-57-3; **5**, 24806-58-4; **7**, 24806-59-5; **9**, 24806-60-8; **11**, 24806-61-9; **13** 24806-62-0; **22**, 21529-86-2; **24**, 24806-64-2; **28**, 24807-41-8; **29**, 24806-65-3; **30**, 24807-42-9; **31**, 15018-12-9; **32**, 24806-66-4; **33**, 24807-44-1; **34**, 24807-45-2; **35**, 24806-67-5; **36**, 24807-46-3; **37**, 24807-47-4; **39**, 24807-48-5; **41**, 24807-49-6; **44**, 24806-68-6; **46**, 24806-69-7; 2-methylthio-1-tetralone, 24807-50-9; 2-methylthio-*m*-methoxyacetophenone, 24807-51-0; *m*-methoxybenzyl methyl sulfide, 24807-52-1; ethyl *o*-(methylthio)methylbenzoate, 24807-53-2; *o*-(methylthio)methylbenzyl alcohol, 24807-54-3.

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Photolysis of Triarylsulfonium Salts in Alcohol[1]

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Various triarylsulfonium salts have been subjected to photolysis in methanol and ethanol solutions, light of wavelength 2537 Å being used. The major products are aromatic hydrocarbons, aryl halides, aryl alkyl ethers, biaryls, diaryl sulfides, diaryl sulfoxides, and Brønsted acids. Diaryl disulfides and arylthiols are also produced, but it has not been possible to determine the yields of these compounds. The available evidence indicates that two major, primary photochemical reactions are taking place concurrently. One gives rise to a diarylsulfinium cation radical plus an aryl radical, and the other represents an electron-transfer reaction in which a triarylsulfur radical and a halogen atom are produced. The latter reaction is of greatest importance when triarylsulfonium iodides are photolyzed.

A complex mixture of products is produced when a triarylsulfonium salt is subjected to photochemical decomposition in alcohol solution. For example, photolysis of triphenylsulfonium chloride in ethanol solution for 61 hr, light of wavelength 2537 Å being used, gives benzene (10%), chlorobenzene (1%), phenetole (9%), biphenyl (1%), diphenyl sulfide (26%), diphenyl sulfoxide (2%), and hydrogen chloride (57%); unreacted triphenylsulfonium chloride is recovered in 34% yield. The photolysis of triphenylsulfonium chloride in methanol for 61 hr at 2537 Å affords benzene (10%), chlorobenzene (0.5%), anisole (11%), diphenyl (2%), diphenyl sulfide (30%), benzyl alcohol (0.2%), diphenylsulfoxide (2%), methylal (11%), and hydrogen chloride (49%); 33% of the starting sulfonium salt is recovered unchanged. Data for numerous additional photodecompositions of triarylsulfonium salts are given in Tables I and II. It is obvious that either aryl radicals or aryl cations are produced at some stage of these reactions, and four different pathways may be considered for the primary photochemical reactions.

$$X^- + \text{solvent} \overset{h\nu}{\rightleftharpoons} X\cdot + e^-(\text{solv})$$

$$Ar_3S^+ + e^-(\text{solv}) \rightleftharpoons Ar_3S\cdot + \text{solvent}$$

$$Ar_3S\cdot \rightleftharpoons Ar_2S + Ar\cdot \qquad \text{(a)}$$

$$Ar_3S^+ \overset{h\nu}{\rightleftharpoons} Ar_2S + Ar^+ \qquad \text{(b)}$$

$$Ar_3S^+ \overset{h\nu}{\rightleftharpoons} (Ar_2S\cdot^+, Ar\cdot) \longrightarrow Ar_2S\cdot^+ + Ar\cdot \qquad \text{(c)}$$

$$Ar_3S^+ + X^- \overset{h\nu}{\rightleftharpoons} Ar_3S\text{–}X \rightleftharpoons (Ar_3S\cdot, X\cdot) \longrightarrow Ar_3S\cdot + X\cdot$$

$$Ar_3S\cdot \rightleftharpoons Ar_2S + Ar\cdot \qquad \text{(d)}$$

Mechanism a, in which a solvated electron[2] is formed as a reactive species, might be expected to occur most readily when an easily photooxidized anion is present.[3] Since essentially the same products (and ratios of products) are formed from both triphenylsulfonium chloride (expt 11, Table II) and triphenylsulfonium fluoroborate (expt 15, Table II), this mechanism appears to be an unlikely one. It can also be ruled out as a major pathway leading to products because the presence of nitrate ion (expt 4, 6, 14, 24) or of iodobenzene (expt 9) does not influence products or product ratios. These additives are known to scavenge solvated electrons and would be expected to inhibit the reaction if mechanism a were operative.[3b] Furthermore, HX is generated during each overall reaction, and the solvated electrons would be scavenged rapidly by protons.[3b,4]

Pathway b, which represents a photochemical heterolytic dissociation of a C–S bond to give an aryl cation plus a diaryl sulfide, can be ruled out on the basis that the presence of iodine (expt 27, Table II), oxygen (expt 25, Table II), or diphenyl disulfide (expt 17, Table II) markedly inhibits the formation of benzene, halobenzene, anisole, and biphenyl. Since these additives are radical scavengers and would have no effect on the formation of an aryl cation by mechanism b,[5] it can be concluded that such an ion is not being produced in the primary photochemical process.[6]

Mechanism d represents an electron-transfer reaction similar to those postulated to occur in related reaction systems.[1,7] If such a mechanism were operative, the yields of aromatic hydrocarbon, aryl halide, and diaryl sulfide would correspond to the ease with which the counteranion can give up an electron to the associated acceptor cation. Thus, the amounts of these products should increase with change of anion in the order BF_4^-, NO_3^-, $C_2H_3O_2^-$, $Cl^- < Br^- < I^-$,[3a,8] provided that solvent effects remain roughly the same. When ethanol is used as the solvent and a triphenylsulfonium salt as substrate, a good correlation between apparent photoreducing power of the anion and the yields of benzene, diphenyl sulfide, and phenyl halide is observed (expt 1, 2, 3, and 4, Table I).[9] When methanol, which is more

(1) A preliminary report of a small portion of this work has been published: J. W. Knapczyk and W. E. McEwen, *J. Amer. Chem. Soc.* **91**, 145 (1969).

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(3) (a) L. E. Orgel, *Quart. Rev.*, **8**, 422 (1954); (b) M. Anbar, "Reactions of the Hydrated Electron," ref 2, p 55.

(4) L. M. Dorfman, "The Solvated Electron in Organic Liquids," ref 2, p 36.

(5) D. F. DeTar and M. N. Turetzky, *J. Amer. Chem. Soc.*, **77**, 1745 (1955).

(6) Evidence that the effect of these additives cannot be attributed to a quenching of excited sulfonium cations will be presented subsequently.

(7) (a) L. Horner and J. Dörges, *Tetrahedron Lett.*, 763 (1965); (b) C. E. Griffin and M. L. Kaufman, *ibid.*, 769, 773 (1965); (c) T. D. Walsh and R. C. Long, *J. Amer. Chem. Soc.*, **89**, 3943 (1967); (d) J. W. Knapczyk, G. H. Wiegand, and W. E. McEwen, *Tetrahedron Lett.*, 2971 (1965).

(8) (a) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," Wiley, New York, N. Y., 1966 p 268; (b) H. Friedman, *J. Chem. Phys.*, **21**, 319 (1953); (c) P. Pringsheim, "Fluorescence and Phosphorescence," Interscience, New York, N. Y., 1963, p 328. The position of BF_4^- in this list represents an approximation.

(9) The presence of nitrate ion appears to catalyze the formation of benzene when ethanol is used as the solvent (expt 4 and 6, Table I) but not when methanol is the solvent (expt. 12, 14 and 24, Table II). That the increased yield of benzene observed in expt 6 (Table I) is not attributable to the presence of lithium ion or to an increase in the ionic strength of the medium is demonstrated by the results of expt 5, which show that the addition of lithium chloride has little effect on the yields of the products cited above. The influence of nitrate ion may not be due to its effect on a primary reaction but rather to its inhibitory effect on a secondary reaction that would otherwise consume the precursor of benzene.

TABLE I[a,b]

IRRADIATION OF TRIPHENYLSULFONIUM SALTS FOR 61 HR IN ETHANOL

Expt	X	Additive	C_6H_6	C_6H_5X	$C_6H_5OC_2H_5$	C_6H_5–C_6H_5	$(C_6H_5)_2S$	Recovered $(C_6H_5)_3S^+X^-$	H^+	$(C_6H_5)_2$–S=O	Footnote
1	Cl		10	1.2	9	1.2	26	34	57	2	*c*
2	Br		23	7	4	1.4	36	24			*d*
3	I		31	36	2	1.4	52	~10			*e*
4	NO_3		34		9	1.4	28	29			*d*
5	Cl	7.0×10^{-4} LiCl	10	1.2	9	1.2	27		49		*f*
6	Br	7.0×10^{-4} $LiNO_3$	45	7	4	1.4	36		15	1	c, *f*
7	Br	1.4×10^{-3} CH_3CHO	32	7	5	1.9	33	41	51		*f*
8	Br	7.0×10^{-4} $(C_6H_5)_2S$	21			0.5	44[g]	51			*f*, *d*
9	I	7.0×10^{-4} C_6H_5I	32		2	0.8	53	10[h]			*f*, *d*
10	$(C_6H_5)_2S$		17			0.4	72	0	6		*i*

[a] We elected not to express percentage yields in terms of amount of sulfonium salt reacted because of the uncertainty in determining the amount of unreacted sulfonium salt in some cases. [b] Many of the reactions summarized in this table were run in duplicate and some in triplicate to determine reproducibility, which was excellent. [c] Thiophenol could not be detected in these mixtures. [d] When no number appears under H^+ it means that the mixture was not titrated. Brønsted acids were produced in every experiment. [e] Iodine was produced. The sulfonium salt was isolated in the form of the triiodide.[h] [f] Values of additives in moles. [g] Based on 0.0014 mol. [h] Isolated as the triiodide, mp 137–138 [lit. mp 137.5–138: W. A. Bonner, *J. Amer. Chem. Soc.*, 74, 5078 (1952)]. [i] Control experiment.

polar than ethanol,[10] is used as solvent, the correlation also holds for the tri-*p*-tolylsulfonium salts, and, with the exception of the formation of benzene in expt 13 (Table II), for the triphenylsulfonium salts (expt 11, 12, 13, 28, and 29, Table II). However, the main drawback of mechanism d as the major primary photochemical process is that it offers no reasonable way to account for the large amounts of Brønsted acids formed in most of the reactions.

Mechanism c consists of a photochemical homolytic cleavage of the triarylsulfonium salt to give an aryl radical and a diarylsulfinium salt.[11] The diarylsulfinium cation might be expected to undergo further reactions, depending on the availability of the various reagents, by the following mechanisms, four of which (e through h) give rise to Brønsted acids.

$$Ar_2S\cdot^+ \rightleftharpoons Ar\dot{S}\cdot + Ar^+$$

$$Ar^+ + ROH \longrightarrow ArOR + H^+ \quad (e)$$

$$Ar_2S\cdot^+ + H\text{–}CH_2OH \longrightarrow Ar_2S^+H + \cdot CH_2OH$$

$$Ar_2S^+H \rightleftharpoons Ar_2S + H^+ \quad (f)$$

$$Ar_2S\cdot^+ + \cdot CH_2OH \longrightarrow Ar_2S + {}^+CH_2OH$$

$${}^+CH_2OH \longrightarrow CH_2O + H^+ \quad (g)[12]$$

$$Ar_2S\cdot^+ + \cdot CH_2OH \longrightarrow Ar_2S^+H + CH_2O$$

$$Ar_2SH^+ \longrightarrow Ar_2S + H^+ \quad (h)[11a]$$

$$Ar_2S\cdot^+ + X^- \longrightarrow Ar_2S + X\cdot \quad (i)[11a]$$

$$Ar_2S\cdot^+ + O_2 \longrightarrow Ar_2S^+\text{–}O\text{–}O\cdot$$

$$Ar_2S^+\text{–}O\text{–}O\cdot + CH_3OH \longrightarrow Ar_2S^+\text{–}O\text{–}O\text{–}H + \cdot CH_2OH$$

$$Ar_2S^+\text{–}O\text{–}O\text{–}H\ X^- \longrightarrow Ar_2\dot{S}\text{–}O\text{–}O\text{–}H + X\cdot$$

$$Ar_2\dot{S}\text{–}O\text{–}O\text{–}H \longrightarrow Ar_2S^+\text{–}O^- + \cdot OH \quad (j)[13]$$

$$Ar_2S\cdot^+ + I_2 \rightleftharpoons Ar_2S^+I + I\cdot \quad (k)$$

$$C_6H_5\text{–}S\text{–}S\text{–}C_6H_5 \overset{h\nu}{\rightleftharpoons} 2C_6H_5S\cdot$$

$$Ar_2S\cdot^+ + C_6H_5S\cdot \longrightarrow Ar_2S^+\text{–}S\text{–}C_6H_5 \quad (l)$$

The inhibition of formation of alkyl aryl ether when radical scavengers (*e.g.*, oxygen, iodide ion, and the phenylthiyl radical[11a]) are present can be explained in terms of reactions i, j, k, and l; *i.e.*, the scavengers intercept the diarylsulfinium cation radical before it has a chance to react by pathways e, f, g, and h.

A substantial amount of diphenyl sulfoxide was produced in the experiment where the reaction mixture was exposed to oxygen (expt 25, Table II). Although some of the sulfoxide may have arisen by photooxidation of diphenyl sulfide produced in the reaction mixture, most of it must have been formed from another precursor. The evidence for this statement consists of the observation that the yield of diphenyl sulfoxide in expt 25 (Table II) was 13%, but the yield of diphenyl sulfide

(10) The dielectric constant for methanol at 20° is 33.6 as against 25.1 for ethanol.[4]

(11) (a) U. Schmidt, "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience, New York, N. Y., 1967, p 75; (b) H. J. Shine, ref 11a, p 93; (c) S. G. Cohen, ref 11a, p 33.

(12) A similar reaction has been reported to occur with a phenyl radical as the hydrogen abstracting agent.[5] However, if phenyl radicals produced by mechanism d were responsible for the generation of the Brønsted acids, there would be a correspondence between the molar amounts of acid and benzene obtained. Clearly, there is no such relationship, as the molar amount of acid greatly exceeds that of benzene in each of the reactions of the triphenylsulfonium salts.

(13) An alternative mechanism for the formation of the diaryl sulfoxide is the following.[11a]

$$Ar_2S\cdot^+ + \cdot OH \rightleftharpoons Ar_2S^+\text{–}OH$$

$$Ar_2S^+\text{–}OH \rightleftharpoons Ar_2S^+\text{–}O^- + H^+$$

It is also possible that hydroxyl radicals arise by the following pathway in the irradiated reaction mixture.

$$O_2 + 2CH_3OH \overset{h\nu}{\longrightarrow} H_2O_2 + 2\cdot CH_2OH$$

$$H_2O_2 \overset{h\nu}{\rightleftharpoons} 2\cdot OH$$

The bond dissociation energies of H–CH_2OH and H–$C(CH_3)HOH$ are 24 and 21 kcal/mol, respectively, at 298°K.[5a] Thus, energy considerations for these hydrogen abstraction reactions on methanol and ethanol would appear to be highly favorable.

TABLE II[a]

IRRADIATION OF $(p\text{-}RC_6H_4)_3S^+X^-$ FOR 61 HR IN METHANOL

Expt	R	X	Additive	C_6H_5R	p-X-C_6H_4R	p-R-$C_6H_4OCH_3$	(p-R-C_6H_4)$_2$	(p-R-C_6H_4)$_2$S	Recovered (p-RC_6H_4)$_3$S$^+X^-$	H^+	p-R-C_6H_4-CH_2OH	(p-R-C_6H_4)$_2$-S=O	CH_2-$(OCH_3)_2$	Footnote
11	H	Cl		10	0.5	11	2.0	30	33	49	0.2	2	11	
12	H	Br		13	2	7	1.0	37	30	43			17	
13	H	I		10	47	6	0.8	43		4	t	0.3	16	*b, c, d*
14	H	NO_3		11		10	1.1	38	39					*e*
15	H	BF_4		11		9	1.1	34	38			3	15	*f, g*
16	H	$OCC_6H_5 \cdot 2H_2O$		9		12	1.6	35					14	*e*
17	H	Cl	3.5×10^{-4} $(C_6H_5S)_2$	3	0.1	2		22	75	52			6	*h, i*
18	H	Br	Pyrex vessel	8	0.5	t	0.1	12	78	9	t			*b, j*
19	H	Br	1.4×10^{-3} H_2O	15	2	9	1.7	33	31	44	t		19	*b, i*
20	H	Br	1.4×10^{-3} $CH_2(OCH_3)_2$	12	3	7	2	29	39	42	t			*b, i*
21	H	Br	7.0×10^{-4} $(C_6H_5)_2S$	13	2	3	0.8	60	53	30			24	*g, i*
22	H	Br	7.0×10^{-4} $NaOCOCH_3$	14	2	8	2.2	36			0.4	0.3	2	*e, i*
23	H	Br	7.0×10^{-4} $NaOCOC_6H_5$	17	2	7	2.2	37			0.4		2	*e, i*
24	H	Br	7.0×10^{-4} $LiNO_3$	13	2	2	1.1	38	33					*e, i*
25	H	Br	O_2	6	5	0.6	0.5	32	26	51	t	13	41	*b, k*
26	H	I	7.0×10^{-4} NaI	9	70	3	0.4	48		2	t	0	19	*b, c, i*
27	H	NO_3	7.0×10^{-4} I_2	2	43	t	0.2	34		52		2	102	*d, i*
28	CH_3	Br		30	3	8	4	43	13	55			21	
29	CH_3	I		33	58	5	2	47	0	16			21	c
30	$(C_6H_5)_2S$			13		0	1	78						*l, e*
31	$(C_6H_5)_2S$		O_2					4				6		*m, n, k, e, j*
32	H	Br		11	3	6	1.4	27	44	36	t		14	*o*

[a] All reactions except expt 17 produced a solid yellow substance that precipitated on the sides of the reaction vessel. In all reactions several unidentified low-boiling and high-boiling products were also produced. [b] t = trace amount. [c] Iodine was also produced and isolated as triphenylsulfonium triiodide. [d] Methyl iodide was not found. [e] When no number appears under H^+ it means that the mixture was not titrated. [f] An insoluble polymer film formed. [g] Thiophenol not detected. [h] 26% (based on 0.0007 mol) thiophenol found. [i] Values of additive in moles. [j] Control experiment. [k] The solutions were saturated with oxygen and sealed in an atmosphere of pure oxygen. [l] An insoluble oil was also produced. [m] Percentages based on 0.00035 mol of starting sulfide. [n] Artificial mixture also containing 5×10^{-5} mol of benzene, 2×10^{-6} mol of chlorobenzene, 1×10^{-5} mol of biphenyl, 2×10^{-4} mol of methylal, 2×10^{-4} mol of hydrochloric acid. [o] Reaction period 13.5 hr.

decreased only 5% as against the results of expt 12 (Table II). Also, in a control experiment in which diphenyl sulfide was irradiated in the presence of oxygen and an artificial mixture of reaction products, the yield of diphenyl sulfoxide was only 6% (expt 31, Table II). Thus, we suggest that much of the diphenyl sulfoxide produced in expt 25 arose by mechanism j or else by the alternative pathway depicted in footnote 13.[14]

As an alternative to pathway e for the formation of alkyl aryl ethers, consideration must be given to the possibility that an aryl radical adds to the oxygen atom of formaldehyde or acetaldehyde, generated as shown in eq g and h, to give a new radical, ArOĊHR, which then forms the ether by a suitable hydrogen abstraction reaction.[15] This possibility is ruled out on the basis of the fact that the addition of relatively large amounts of acetaldehyde (expt 7, Table I) or methylal (expt 20, Table II) to the reaction mixtures did not bring about any increase in the yields of ethers.

All of the reaction mixtures became acidic as the reaction progressed. However, there were significant differences in the amounts of titratable acids produced, depending on the nature of the anion present.[16] Specifically, the amount of acid produced was least when iodide ion was present, intermediate in amount when bromide ion was present, and greatest with chloride. Since the Brønsted acids presumably arise *via* mechanism c followed by e through h, the anion effect implies strongly that pathway d competes with c as the primary process. As mentioned previously, pathway d would increase in importance with change of anion in the order $Cl^- < Br^- < I^-$ and would not set in motion subsequent reactions which would produce any significant amounts of Brønsted acids.[12] In other words, the amount of Brønsted acid produced is a good measure of the extent

(14) These results also provide evidence that quenching of photoexcited triarylsulfonium cation is not a likely explanation for the inhibition of certain of the reactions when the additives are present.

(15) (a) M. S. Kharasch, D. Schwartz, M. Zimmermann, and W. Nudenberg, *J. Org. Chem.*, **18**, 1051 (1953); (b) F. F. Rust, F. H. Seubold, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **70**, 3258 (1948); (c) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 238 (1953).

(16) The presence of buffers did not produce any significant effect on the ratios of products (expt 12, 16, 22, and 23, Table II). It should also be noted that a small amount of Brønsted acid is produced by the photodecomposition of the diaryl sulfide which is produced in the major sequences of reactions (expt 10, Table I).

of reaction proceeding by pathway c as the primary step. Indeed, in many of the experiments there is a good correspondence between the molar amounts of acid and the combined molar amounts of, for example, anisole and methylal formed. Specifically, 1 mol of acid should be produced/mol of anisole (eq e) and 2 mol of acid/mol of methylal (eq f, g, and h) produced. Thus, in expt 12 (Table II) a 41% yield of acid would be anticipated on the basis of this reasoning as against 43% actually found.

A comparison of the results of the reactions of tri-*p*-tolylsulfonium bromide and iodide in methanol solution (expt 28 and 29, Table II) with those of triphenylsulfonium bromide and iodide (expt 12 and 13, Table II) reveal that the former give a larger ratio of aromatic hydrocarbon plus biaryl to aryl halide than the latter. This is probably a reflection of the greater stability of the tri-*p*-tolylsulfur radical as against the triphenylsulfur radical.[17] It is a reasonable assumption that the radicals produced by mechanism d are initially paired; *i.e.*, they exist in a solvent cage. The more stable the radicals that make up the radical pair, the greater is the likelihood of the radicals becoming free from one another and reacting with the solvent or other molecules external to the solvent cage, these reactions producing aromatic hydrocarbons and biaryls, among other products. This sequence of reactions starts with pathway m. On the other hand, when the radical pair consists of more reactive radicals, they tend to react within the solvent cage to produce an aryl halide plus a diaryl sulfide, as shown in the reaction pathway n.

$$(Ar_3\ddot{S}\cdot, X\cdot) \rightleftharpoons Ar_3\ddot{S}\cdot + X\cdot$$

$$Ar_3\ddot{S}\cdot \longrightarrow Ar_2S + Ar\cdot \qquad (m)$$

$$(Ar_3\ddot{S}\cdot, X\cdot) \longrightarrow Ar_2S + ArX \qquad (n)$$

In the reaction of the triarylsulfonium iodides, some iodine is produced by photochemically initiated redox reactions. When iodine is formed in this manner, at least some of the aryl iodide produced arises by the reaction pathway o.[8,18] In fact, since aryl iodides are formed apparently at the expense of aromatic hydrocarbons and biaryls in the reactions of the triarylsulfonium iodides, pathway o might represent a substantial source of the aryl iodides produced.

$$2I\cdot \rightleftharpoons I_2$$

$$Ar\cdot + I_2 \rightleftharpoons ArI + I\cdot \qquad (o)$$

Varying amounts of resinous materials were formed in each of the photochemical experiments. Thus, it is difficult to analyze the data with respect to material balance considerations, especially with regard to the organosulfur compounds. As a result of the photolysis of tri-*p*-tolylsulfonium iodide in methanol solution (expt 29, Table II), for example, the combined yield of toluene, *p*-iodotoluene, *p*-methoxytoluene, and di-*p*-tolyl was 98%, but the yield of di-*p*-tolyl sulfide was only 47%. Furthermore, no di-*p*-tolyl sulfoxide was found, nor was any tri-*p*-tolylsulfonium iodide recovered.

(17) A similar argument was used to explain differences in reactivities of tri-*p*-tolylsulfonium and triphenylsulfonium salts in reactions with sodium alkoxides.[1,7d]

(18) Under the conditions employed in these experiments, a significant amount of iodide ions would be converted to iodine atoms. Since hydrogen abstraction reactions of the iodine atoms would be reversible, the concentration of iodine atoms would probably be appreciable at all times.

A partial explanation for these results is the fact that the diaryl sulfide itself undergoes a photochemical reaction. By way of illustration, irradiation of diphenyl sulfide under the same conditions as employed for the tri-*p*-tolylsulfonium iodide reaction afforded benzene in 13% yield and biphenyl in 1% yield; diphenyl sulfide was recovered in 78% yield (expt 30, Table II).[19]

Trace amounts of thiophenols and diaryl disulfides were found in many of the reaction mixtures.[20] Diphenyl sulfoxide was found in yields ranging from 0.3 to 3.0% even in those systems where precautions were taken to exclude oxygen of the air (expt 1 and 6, Table I and 11, 13, 15, 22, and 27, Table II).

Inasmuch as diaryl disulfides and thiophenols absorb strongly in the 2537-Å region of the ultraviolet spectrum, and since arylthiyl radicals are produced from such compounds under these conditions as shown, for example, in eq p,[21] it is probable that such radicals, which are also formed by irradiation of diaryl sulfides as shown in eq q,[22] persist for an appreciable period of time. This would be so even in a solvent which is susceptible to hydrogen abstraction by such radicals owing to the continual renewal of the arylthiyl radicals, as shown in eq r.[23] This permits aromatic radical sub-

$$Ar\text{–}S\text{–}S\text{–}Ar \overset{h\nu}{\rightleftharpoons} 2\ ArS\cdot \qquad (p)$$

$$Ar_2S \overset{h\nu}{\rightleftharpoons} ArS\cdot + Ar\cdot \qquad (q)$$

$$ArS\cdot + CH_3OH \rightleftharpoons ArSH + \cdot CH_2OH$$

$$ArSH \overset{h\nu}{\rightleftharpoons} ArS\cdot + H\cdot \qquad (r)$$

stitution reactions of the types shown in eq s and t to occur during extended irradiation periods and probably accounts for the formation of organosulfur compounds of high molecular weight, which are not detected by vapor phase chromatography.[24,25]

(19) One of the referees suggested that product ratios (abundances) or individual yields, adjusted for recovered triarylsulfonium salt, the limiting reactant, should be used to compare the results of these experiments rather than conventional yields, which were actually used. Since we are not sure of the origin of some of our products, it is our opinion that the use of unrecovered triarylsulfonium salt as the "limiting reactant" may be misleading. Furthermore, on the basis of yields and product ratios, calculated according to the suggestions of the referee, we see no reason to change our conclusions about mechanisms of reaction.

(20) Through control experiments, we found that small amounts of diphenyl disulfide could not be detected by vapor phase chromatography inasmuch as the compound underwent decomposition at the injection port of the gas chromatograph. A partial analysis based on its decomposition products was possible only when the compound was present in large amount. Attempts to determine quantities of thiophenols and diaryl disulfides in the reaction mixtures by application of thin layer chromatography were unsuccessful owing to the complexity of the mixture.

(21) (a) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill, New York, N. Y., 1962, p 42; (b) J. G. Calvert and J. N. Pitts, ref 8a, p 488.

(22) (a) L. Horner and J. Dörges, *Tetrahedron Lett.*, 757 (1963); (b) N. Kharasch and A. I. A. Khodair, *Chem. Commun.*, 98 (1967).

(23) (a) J. G. Calvert and J. N. Pitts, ref 8a, p 490; (b) W. E. Haines, G. L. Cook, and J. S. Ball, *J. Amer. Chem. Soc.*, **78**, 5213 (1956).

(24) Solutions of dimesityl disulfide in 2-propanol in the presence of benzophenone are readily converted to an equilibrium mixture of about 70% mesitylthiol and 30% dimesityl disulfide when irradiated: S. G. Cohen, ref 11a, p 42. Apparently the presence of methyl groups in the *ortho* and *para* positions inhibit aromatic radical substitution reactions of the types depicted in eq s and t.

(25) Since thiophenols are known to give rise to solvated electrons in suitable solvents, the following pathway for the generation of arylthiyl radicals is also a possibility.

$$ArSH + \text{solvent} \overset{h\nu}{\rightleftharpoons} Ar\dot{\ddot{S}}^{+}H + e^{-}\ (\text{solvated})$$

$$Ar\dot{\ddot{S}}^{+}H \rightleftharpoons ArS\cdot + H^{+}$$

Cf. L. I. Grossweiner and H. I. Joschek, ref 2, p. 279.

$$2ArS\cdot \longrightarrow ArSArSH \qquad (s)^{26}$$

$$ArS\cdot + ArSArSH \longrightarrow ArSH + ArSArS\cdot, \textit{ etc.}$$

$$ArH + ArSArS\cdot \longrightarrow \text{(ArSArS, H)}, \textit{ etc.} \qquad (t)^{22b}$$

All of the photochemical reactions listed in Tables I and II except the last one (expt 32, Table II) were allowed to continue for a period of 61 hr. In expt 32, the reaction mixture was irradiated for only 13.5 hr. Comparison of the results of this experiment with those of expt 12 (Table II) reveals relatively little difference in the yields of the various products. Nevertheless, a significant quantity of unreacted triphenylsulfonium bromide was recovered even after the 61-hr period of irradiation. A possible explanation is that, owing to the formation of products which strongly absorb light of the wavelength used in the irradiation relatively early in the period of irradiation, much of the photochemical energy needed for the primary process is unavailable at a later time. For example, the presence of diaryl disulfides or arylthiols and the occurrence of reactions of the types depicted in eq p and r could cause inhibition of the primary processes c and d. Indeed, when diphenyl disulfide was added to a typical reaction mixture (expt 17, Table II), the amount of triphenylsulfonium salt recovered after a 61-hr period of irradiation increased markedly (*cf.* expt 11, Table II).[27]

The addition of diphenyl sulfide to the solutions of triphenylsulfonium bromide prior to irradiation also leads to a marked increase in the recovery of starting material (*cf.* expt 2 and 8, Table I, and 12 and 21, Table II). A reversal of eq d could account for this result. A similar explanation has been suggested for analogous results observed in the photodecomposition of phosphonium salts.[7b] Also, some evidence has been presented in the literature for the addition of an alkoxyl radical to diphenyl sulfide to give

$$(C_6H_5)_2\dot{S}OR$$

as an unstable intermediate in certain reactions.[28]

(26) Y. Schaafsma, A. F. Bickel, and E. C. Kooyman, *Tetrahedron*, **10**, 76 (1960).

(27) Actually, it is not known whether diphenyl disulfide or the products of its photochemical dissociation are acting as filters, or whether the disulfide is quenching an excited state of one of the primary photochemical decomposition reactions.

(28) R. J. Gritter and D. J. Carey, *J. Org. Chem.*, **29**, 1160 (1964).

Experimental Section

All of the sulfonium salts were prepared as described in a previous paper,[1] with the exception of triphenylsulfonium benzoate.

Triphenylsulfonium Benzoate Dihydrate.—To 3.65 g (0.0095 mol) of triphenylsulfonium iodide dissolved in 40 ml of methanol was added 2.2 g (0.01 mol) of silver oxide. The mixture was allowed to stir rapidly for 4 hr in the dark. The precipitate of silver iodide and unreacted silver oxide was removed by filtration, and to the clear filtrate was added a solution of 1.2 g (0.01 mol) of benzoic acid in 5 ml of methanol. The solution was evaporated to dryness. The resulting oil was induced to crystallize from methylene chloride–ether mixtures. The yield of the purified substance, mp 288–289°, was 0.91 g (20%).

Anal. Calcd for $C_{25}H_{24}SO_4$: C, 68.46; H, 5.99; S, 7.31. Found: C, 68.48; H, 5.90; S, 7.29.

Irradiation of Triarylsulfonium Salts.—The sulfonium salts, 7.00×10^{-4} mol, and the appropriate additives were dissolved in 3.00 ml of the appropriate anhydrous solvent[29] which had previously been deaerated by bubbling a fine stream of dry, oxygen-free nitrogen through the refluxing solution for 4 hr. The solutions were sealed under nitrogen in 12-mm quartz tubes and irradiated by a bank of sixteen Rayonet photochemical reactor lamps no. RPR of which 90% of the intensity of the light is of wavelength 2537 Å. Each solution was homogeneous at the start of reaction. At the end of the reaction period the tubes were opened and the contents were analyzed directly by gas chromatography, an F & M Model 609 flame ionization gas chromatograph being used. To obtain proper separations of the volatile materials, three different columns had to be used: (1) a 6-ft 5% Apiezon L column for most of the components, (2) a 6-ft 20% Carbowax 20M column for determination of methylal, and (3) a 6-ft 15% Ucon 50 column for determination of bromobenzene in the presence of phenetole. The concentration of Brønsted acids was determined by pipetting a 1.00-ml aliquot of the sample into 50 ml of water and titrating to the phenolphthalein end point with 0.1500 *N* sodium hydroxide solution. The amount of unreacted sulfonium salt was found by adding a 1.00-ml aliquot of the reaction mixture to 45 ml of anhydrous ether. After several hours the solution was decanted from the crystals that had formed, and the crystals were washed with 40 ml of anhydrous ether, dried, and weighed. In most cases a melting point and an infrared spectrum were taken of the solid to confirm its identity.

Registry No.—Triphenylsulfonium benzoate, 25183-63-5. Table I—expt 1 (salt), 4270-70-6; 2 (salt), 3353-89-7; 3 (salt), 3744-08-9; 4 (salt), 19600-48-7; 10 (salt), 139-66-2. Table II—expt 15 (salt), 437-13-8; 28 (salt), 3744-11-4; 29 (salt), 22417-23-8.

Acknowledgment.—This work was supported by a grant from the National Science Foundation. Miss Rebecca Dike carried out many of the vpc analyses and titrations.

(29) The alcohols were dried by the method of Lund and Bjerrum as described in A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, p 167.

Photocyclizations. I. 4,5-Dihydro-1H-naphth[1,8-*de*]azocin-2(3H)-one

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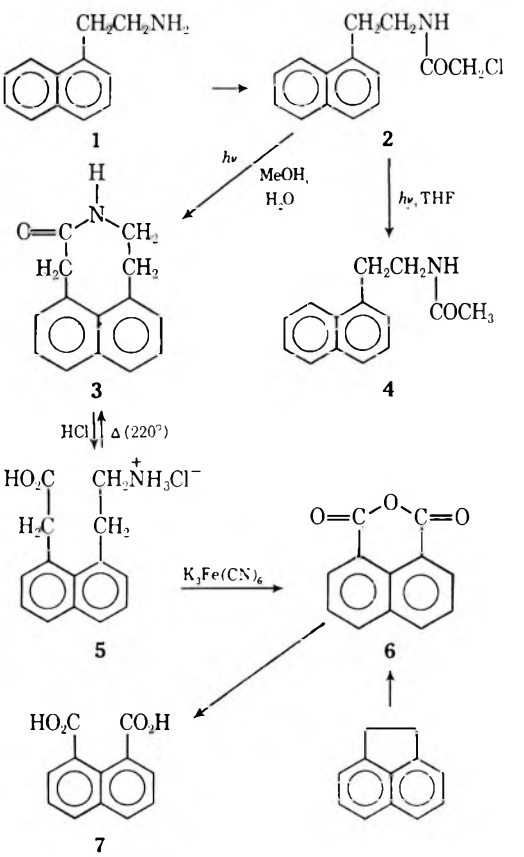
Photolysis of 1-(2-chloroacetamioethyl)naphthalene (2) in aqueous methanol has given naphthazocine 3 in 40–45% yields. The structure of 3, assigned from nmr, uv, ir, and mass spectral data along with steric considerations, was rigorously confirmed by its degradation to 1,8-naphthalic anhydride (6), also obtained from acenaphthene. Photolysis of 2 in tetrahydrofuran gave chiefly hydrogenolysis product 4 and no 3.

The photolysis of N-chloroacetyl derivatives of a variety of pharmacodynamic amines as well as some aromatic amino acids has been studied extensively by Yonemitsu and Witkop.[1-3] Among the many reactions observed, cyclization with release of hydrogen chloride seems to be the major pathway in neutral, aqueous medium leading to the formation of tricyclic indoles, benzazepines, and azaazulenes in yields ranging from 20 to 70%. As part of a study designed to explore the synthetic potentialities of such intramolecular cyclizations, it was of interest to us to examine the behavior of similar compounds incorporating aromatic systems other than a hydroxyphenyl or indole system. In this paper we report the photolysis of 1-(2-chloroacetaminoethyl)naphthalene (2) and the characterization of products obtained therefrom.

1-(2-Aminoethyl)naphthalene (1) prepared by the method of Schleigh, *et al.*[4] (or less satisfactorily by reduction of 1-naphthylacetonitrile with metal hydrides), was best converted to 2 in a nonpolar solvent in the presence of powdered potassium carbonate, with either chloroacetyl chloride or the anhydride. Irradiations of 2 were generally carried out in dilute solutions through which nitrogen was bubbled to remove dissolved oxygen. Vycor filters ($\lambda > 210$ mμ) were used in conjunction with a high-pressure mercury immersion lamp. In a methanol–water solution, the chloroacetamide, 2, was rapidly consumed and a photoproduct, 3, was isolated to which the empirical formula $C_{14}H_{13}NO$ could be assigned on the basis of its mass spectrum and combustion analyses. The ir spectrum of 3 taken in condensed phase showed carbonyl absorption at 1670 cm^{-1} and an NH band at 3170 cm^{-1}, both at higher frequencies than those of the corresponding 2. In the uv spectrum of 3 was a main band at 287 mμ compared with 281 for 2, a bathochromic shift attributable to the transverse polarization of the naphthalene nucleus.[5]

A 100-MHz nmr spectrum of 3 in dimethyl sulfoxide-d_6 showed signals for six aromatic protons with two centered at δ 7.75, and the other four at δ 7.35, indicative of two α and four β protons. The slightly broadened singlet at δ 7.1 which vanished upon shaking with D_2O was apparently due to the NH proton. Signals from the six alicyclic protons are not clearly defined; they appeared as a very broad band in the region of δ 3.0–3.9. The broadness of lines may be due in part to overlapping or some unresolved long-range coupling; also, it may be a result of incomplete averaging if the rate of ring inversion in the alicyclic system is not very fast.[6]



Thus, it would seem that cyclization of 2 has occurred at one of the α positions of the naphthalene nucleus, and the photoproduct formed could be a derivative of azocine fused to the naphthalene ring at the 1,8 positions, or it could be derivatives of other tricyclic systems formed by cyclization at C-4 or C-5. The last two possibilities were ruled out from spatial considerations, for the bond angles and chain lengths are such that formation of an aliphatic bridge across the naphthalene ring at 1,4 or 1,5 would be virtually impossible. This can be amply demonstrated with models.

A final, unequivocal assignment of structure 3 to the photoproduct was made on the basis of chemical evidence. Refluxing 3 with dilute hydrochloric acid led to an amino acid, 5, whose nmr spectrum showed a now-sharpened methylene signal at δ 4.3 in addition to a symmetrical AA′BB′-type multiplet at 3.15–3.80.

(1) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Amer. Chem. Soc.*, **88**, 3941 (1966).

(2) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *ibid.*, **90**, 776 (1968).

(3) O. Yonemitsu, Y. Okuno, Y. Kanaoka, I. Karle, and B. Witkop, *ibid.*, **90**, 6522 (1968).

(4) W. R. Schleigh, A. Catala, and F. D. Popp, *J. Heterocycl. Chem.*, **2**, 379 (1965).

(5) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1965, p 305.

(6) F. A. L. Anet and M. A. Brown *Tetrahedron Lett.*, 4881 (1967).

When **5** was heated at temperatures above 200° with or without the application of vacuum, a change in crystalline structure took place, and the product isolated was found to be identical with the original photoproduct, **3**, in all respects. The ease with which the thermal ring closure proceeded provided additional support for the *peri*-fused structure in **3**. Numerous attempts were made to oxidize **5** selectively to a known naphthalenedicarboxylic acid. While potassium permanganate, under a variety of conditions, gave mainly a benzenetricarboxylic acid, oxidation with neutral sodium dichromate at 250°, usually found satisfactory for converting dimethylnaphthalenes to naphthalenedicarboxylic acids,[7,8] yielded only naphthoquinone derivatives. Potassium ferricyanide, however, was found to attack slowly the saturated α carbons when used in large excess and in an alkaline medium,[9] leaving the aromatic moiety intact. After 5 days at 75°, compound **5** was thus converted to a thermally unstable dicarboxylic acid which, upon standing or heating, readily lost water to form the anhydride **6**; this was accompanied by a shift of carbonyl frequency from 1690 cm^{-1} to two bands at 1775 and 1740 cm^{-1}. Compound **6** was readily identified as 1,8-naphthalic acid anhydride (**6**) by comparison of its melting point and ir, uv, and nmr spectra with those of an authentic sample, obtained either commercially[10] or by oxidation of acenaphthene.

The photolysis of **2** in an aprotic solvent was also studied. When irradiation was carried out in dilute tetrahydrofuran (THF) solution, the chloroacetamide **3** was consumed at a much slower rate, and the product isolated was mainly 1-(2-acetaminoethyl)naphthalene (**4**) besides some unreacted amide and polymeric materials. Such a dualism of photolytic behavior was also observed by Schaffner[11] and by Witkop[3] who proposed that in nonpolar solvents a radical mechanism initiated by the homolysis of a carbon–halogen bond would be favored; the free radical thus formed could then undergo hydrogen abstraction to yield the acetamide, **4**. In polar solvents, however, cyclization was likely to proceed through an ionic intermediate which, in the present case, was probably preceded by the π–π^* excitation of naphthalene.[12]

Experimental Section

All melting points were determined on a Kofler hot-stage and are uncorrected; ir spectra were recorded with a Perkin-Elmer spectrophotometer, Model 421 (chloroform solutions or KBr pellets). Unless otherwise stated, nmr spectra were taken on a Varian A-60 spectrometer using TMS as internal standard.

1-(2-Chloroacetaminoethyl)naphthalene (2).—A solution of 2.08 g (0.01 mol) of 1 hydrochloride in 10 ml of water was made basic with 2 *N* sodium hydroxide. The separated soil was dissolved in 30 ml of benzene and dried (sodium sulfate). After filtration, the benzene extract was refluxed with 2.08 g of anhydrous potassium carbonate, while a solution of 1.7 g (0.015 mol) of chloroacetyl chloride in 30 ml of benzene was slowly added over 60 min. Heating and stirring were continued for an additional 2 hr. The mixture was cooled and filtered. The filtrate was washed and dried (sodium sulfate). Evaporation of the benzene *in vacuo* left a colorless oil which upon standing yielded 1.9 g (77%) of fine needles: mp 109–110° (benzene–hexane); ν_{max}^{KBr} 3250 (NH), 1645 (amide I), 1560 (amide II) cm^{-1}; nmr ($CDCl_3$) δ 3.15–3.85 (m, 4, AA'BB', $-CH_2CH_2-$), 4.0 (s, 2, $-COCH_2Cl$), 7.60–8.10 (m, 7, aromatic protons).

Anal. Calcd for $C_{14}H_{14}ClNO$: C, 67.86; H, 5.69; N, 5.65. Found: C, 67.90; H, 5.89; N, 5.70.

Photolysis of 2. A. In Aqueous Methanol. 4,5-Dihydro-1H-naphth[1,8-*de*]azocin-2(3H)-one (3).—A solution of 1.24 g (5 mmol) of 1-(2-chloroacetaminoethyl)naphthalene in 300 ml of methanol and 300 ml of water was irradiated for 2 hr with a 200-W Hanovia, high-pressure mercury immersion lamp and a Vycor filter. Nitrogen was bubbled through the solution during the irradiation and the quartz well was kept water cooled. The mixture was evaporated to dryness *in vacuo* at 30°, and the residue was triturated in 5 ml of methanol. After keeping in the cold overnight, the colorless crystals were filtered, 500 mg (47%), mp 275–284°. Recrystallization from methanol–water gave shining platelets: mp 284–286°; ν_{max}^{KBr} 3170 (NH), 1670 (CONH) cm^{-1}. The mass spectrum showed *m/e* 211 (molecular peak), 182 (loss of $NHCH_2$), 169 (loss of CH_2CO).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.55; H, 6.20; N, 6.63. Found: C, 79.74; H, 63.7; N, 6.40.

B. In THF. 1-(2-Acetaminoethyl)naphthalene (4).—A solution of 1.24 g of **2** in 600 ml of THF was irradiated with a 200-W high-pressure mercury lamp at room temperature for 2 hr. After evaporation of the solvent *in vacuo* at 30°, a yellowish oil remained which, upon column chromatography on silica gel (eluted with a 0–5% gradient mixture of ethyl acetate–chloroform), yielded one major product (345 mg, 32%) in addition to 265 mg of unchanged **2**. The former, mp 91°, showed *m/e* 213 (molecular peak), 198 (loss of CH_3), 170 (loss of CH_3CO), and 155 (loss of CH_3CONH); the nmr spectrum ($CDCl_3$) exhibited a sharp singlet at 1.98 ppm corresponding to the three protons of an acetyl group.

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.82; H, 7.08. Found: C, 79.01; H, 6.38.

1-(2-Aminoethyl)-8-carboxymethylnaphthalene Hydrochloride (5).—Compound **3** (211 mg, 1 mmol) and 4 ml of 2 *N* hydrochloric acid were refluxed until a clear solution resulted. Excess acid was removed by vacuum distillation to leave a white crystalline mass weighing 218 mg (82%): mp 194–196° (recrystallization from ethanol–water raised this to 198°); ν_{max}^{KBr} 3050 (NH_3^+), 1710 (COOH) cm^{-1}; nmr (D_2O) 3.15–3.80 (m, 4, AA'BB', $-CH_2CH_2-$), 4.3 (s, 2, CH_2CO), 7.51 (m, 4, β-naphthalene protons), 7.80 (m, 2, α-naphthalene protons) ppm.

Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.25; H, 6.06; N, 5.27. Found: C, 63.41; H, 6.06; N, 5.15.

Thermal Ring Closure of 1-(2-Aminoethyl)-8-carboxymethylnaphthalene Hydrochloride to 4.—When the above hydrochloride, **5** (133 mg, 0.5 mmol), was heated in an oil bath at 220–240°, the crystals melted and subsequently solidified to a grayish mass. Recrystallization from 80% methanol yielded 95 mg (85%) of colorless crystals, mp 282–284°. The ir, uv, and nmr spectra of this compound are superimposable on those of **3** obtained by direct photolysis of **2** in methanol–water. A mixture melting point determination of the two samples showed no depression.

Oxidation of 5 with Potassium Ferricyanide to 1,8-Naphthalic Acid Anhydride (6).—The oxidation was carried out by the general directions of Huisgen and Rietz.[9] A solution of 200 mg (0.75 mmol) of **5**, 40 g of potassium ferricyanide, and 10 g of potassium hydroxide in 160 ml of water was stirred at 70–75° for 5 days. The orange-colored solution was cooled and acidified with concentrated sulfuric acid until acidic to congo red. Extraction of the product was carried out with ether in a continuous extractor for 48 hr. After evaporation of the solvent, a semisolid residue remained which, upon heating with 5 ml of ethanol and chilling, yielded 43 mg (29%) of slightly yellowish needles: mp 274°; mass spectrum *m/e* 198 (molecular peak), 154 (loss of $-C(O)O$), 126 (loss of $-OC(O)O-$); ν_{max}^{KBr} 1775, 1740 cm^{-1} (conjugated cyclic anhydride); λ_{max}^{MeOH} 296 mμ (ϵ 7600).

Anal. Calcd for $C_{12}H_6O_3$ C, 72.71; H, 3.05. Found: C, 72.71; H, 3.15.

This compound proved to be 1,8-naphthalic acid anhydride (**6**) (melting point and ir and uv spectra identical with those of an authentic sample obtained either commercially or by oxidation of acenaphthene). The free dicarboxylic acid, **7**, was prepared by refluxing the above anhydride with 20% potassium hydroxide

(7) L. Friedman, D. L. Fishel, and H. Schechter, *J. Org. Chem.*, **30**, 1453 (1965).

(8) K. B. Wiberg in "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, p 90.

(9) R. Huisgen and U. Rietz, *Tetrahedron*, **2**, 271 (1958).

(10) Purchased from Aldrich Chemical Co., Milwaukee, Wis.

(11) S. Iwasaki and K. Schaffner, *Helv. Chim. Acta*, **51**, 557 (1968).

(12) E. Grovenstein, Jr., T. C. Campbell, and T. Shibata, *J. Org. Chem.*, **34**, 2418 (1969).

followed by acidification at 0°. At higher temperature, the acid is readily cyclodehydrated. Recrystallization from cold acetone–hexane yielded white needles: mp 273°; ν_{max}^{KBr} 2650 (bonded OH), 1690 (COOH) cm^{-1}.

Anal. Calcd for $C_{12}H_8O_4$: C, 66.64; H, 3.72. Found: C, 66.42; H, 3.86.

Oxidation of Acenaphthene. By Potassium Ferricyanide.—Acenaphthene (308 mg, 2 mmol) was oxidized with 30 g of potassium ferricyanide and 10 g of potassium hydroxide in 160 ml of water in the same manner as described previously. After 5 days, the unreacted acenaphthene was removed by filtration and the filtrate acidified. Extraction with ether followed by evaporation yielded 46 mg (23%) of 1,8-naphthalic acid anhydride, mp 274–276°, mass spectrum *m/e* 198. The low yield of the oxidation product was probably due to the insolubility of acenaphthene in water.

Registry No.—**2**, 25055-69-0; **3**, 25055-70-3; **4**, 25055-71-4; **5**, 25055-72-5; **6**, 81-84-5; **7**, 518-05-8.

Reaction of Indole Derivatives with Bromine. Substitution, Oxidation, and Dimerization

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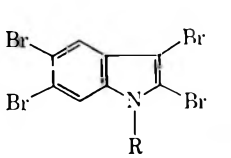
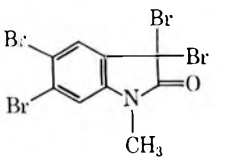
Bromination of 1-methylindole (**1**), 1-methylindole-3-carboxaldehyde (**2**), and ethyl 1-methylindole-3-glyoxylate (**3**), in some solvents and with different mole ratios of bromine to indole, was investigated. Bromination of **1** in acetic acid, when 5:1 mol ratio of reactants was used, gave 2,3,5,6-tetrabromo-1-methylindole (**4a**) and, under somewhat different conditions, 2′,3,5,5′,6,6′-hexabromo-1,1′-dimethyl-2,3′-diindolyl (**6a**); in both cases 3,3,5,6-tetrabromo-1-methyloxindole (**5**) was also isolated. 5-Bromo-1-methylindole-3-carboxaldehyde (**12a**), compound **4a**, and 3,3,5-tribromo-1-methyloxindole (**10a**) were obtained by bromination of **2** (3:1 mol ratio) in acetic acid. Bromination of **3** in acetic anhydride gave mixture of 5- and 6-bromo derivatives (**14a** and **14b**) when a 2.5:1 mol ratio was used, whereas with a 4:1 mol ratio the 5,6-dibromo derivative (**14c**) was isolated in excellent yield. The structure of the compounds was proven on the basis of ir spectra and chemical evidence.

In the course of our work on the chemistry of indoles we have extensively investigated the nitration[1] and, more recently, the bromination[2] of indole derivatives. Although the action of brominating agents upon indoles in different media has been investigated to some extent,[3] comparatively little attention has been devoted to the reaction of indoles with bromine. In a previous paper on this subject we examined the reactions of indole-3-carboxaldehyde, 2-methylindole-3-carboxaldehyde, and ethyl indole-3-glyoxylate with bromine in acetic acid; it was seen that 5 and 6 positions are the normal sites of electrophilic substitution when electron-attracting substituents are present in the β position.[2] In order to extend our knowledge on this topic we have now investigated the bromination of 1-methylindole (**1**), 1-methylindole-3-carboxaldehyde (**2**), and ethyl 1-methylindole-3-glyoxylate (**3**) with bromine.

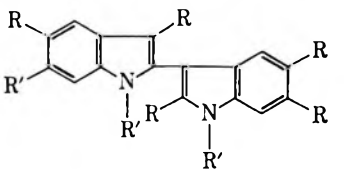
The bromination of **1**, when carried out in acetic acid with an equimolar amount of bromine, did not afford definite products; with a 5:1 mol ratio of reagent to substrate the course of the reaction was dependent on the temperature, and it was possible to isolate satisfactory amounts of solid compounds. When bromine was added to an ice-cold acetic solution of **1**, 1-methyl-2,3,5,6-tetrabromoindole (**4a**) (53% yield) and 1-methyl-3,3,5,6-tetrabromooxindole (**5**) (from the acetic mother liquor; 8.5% yield) were formed. When the reaction was carried out at room temperature, a product was isolated (42.8% yield) for which, on the basis of analytical data, molecular weight determination, and evidence outlined below, we suggest the dimeric structure **6a**; also in this case, **5** was produced (8.5% yield). The proposed structure **6a** was confirmed by its preparation, in 78% yield, through bromination of the dimer **6b**; the latter was prepared both by treating 1-methylindole (**1**) with dioxane–bromine complex in THF solution according to Kunori,[4] and by methylation of 2,3′-diindolyl (**6c**).[5] The latter synthesis of **6b**



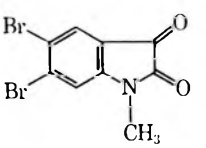
4a, R = CH_3
b, R = H



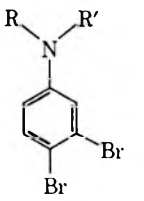
5



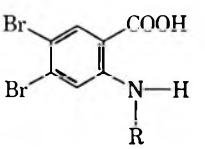
6a, R = Br; R′ = CH_3
b, R = H; R′ = CH_3
c, R = R′ = H



7



8a, R = CH_3; R′ = H
b, R = CH_3; R′ = tosyl
c, R = H; R′ = tosyl



9a, R = CH_3
b, R = H

(1) (a) G. Berti, A. Da Settimo, and O. Livi, *Tetrahedron*, **20**, 1397 (1964); (b) A. Da Settimo and M. F. Saettone, *ibid.*, **21**, 823 (1965); (c) A. Da Settimo and M. F. Saettone, *ibid.*, **21**, 1923 (1965).

(2) A. Da Settimo, M. F. Saettone, E. Nannipieri, and P. L. Barili, *Gazz. Chim. Ital.*, **97**, 1304 (1967).

(3) See, *e.g.*, (a) W. B. Lawson, A. Patchornik, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 5918 (1960); (b) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, **29**, 1206 (1964).

(4) M. Kunori, *Nippon Kagaku Zasshi*, **83**, 836 (1962); *Chem. Abstr*, **59**, 1573c (1963).

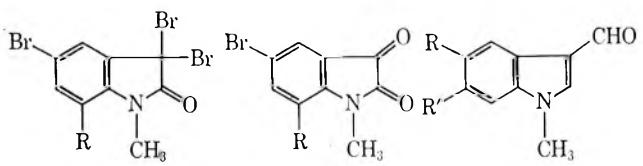
(5) T. E. Young, *J. Org. Chem.*, **27**, 507 (1962).

had the purpose to confirm the previously suggested structure.[4] Compound **6a** gave a negative Ehrlich reaction (both the 2 positions are substituted) and its chromic oxidation gave as the only solid compound, 5,6-dibromo-1-methylisatin (**7**). Unfortunately **7** was isolated in too low yield (less than 50%) to make sure that in both benzene rings the bromine atoms are in the 5,6 positions. On the other hand, as previously shown[2] and corroborated by the present work, positions 5 and 6, at least under our experimental conditions, are substituted more readily than the other positions of the aromatic ring. 5,6-Dibromo-1-methylisatin (**7**) was prepared by reaction of 3,4-dibromo-N-methylaniline (**8a**) with oxalyl chloride in the presence of anhydrous aluminum chloride. The oxidation of **7** with hydrogen peroxide gave 4,5-dibromo-N-methylanthranilic acid (**9a**) which was also obtained by methylation of 4,5-dibromoanthranilic acid (**9b**).[2]

Structure **4a** has been demonstrated by comparison with the compound obtained by methylation of 2,3,5,6-tetrabromoindole (**4b**).[2]

To the minor product of the bromination of **1** has been assigned the structure **5**, because it was hydrolyzed with alkali to 5,6-dibromo-1-methylisatin (**7**) and it gave 4,5-dibromo-N-methylanthranilic acid (**9a**) on oxidation. The reaction of **5** with phenylhydrazine led to a β-phenylhydrazone identical with an authentic sample prepared from **7**. The infrared spectrum of **5** shows a strong C=O peak at 1735 cm^{-1} in good agreement with those found for 3,3,5-tribromo-1-methyloxindole (**10a**) and 3,3,5,7-tetrabromo-1-methyloxindole (**10b**) (1730 and 1725 cm^{-1}, respectively), prepared for comparison through bromination of 1-methyloxindole.

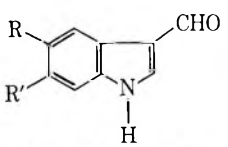
Bromooxindole **10a** can be hydrolyzed to 5-bromo-1-methylisatin (**11a**);[6] analogously **10b** can be hydrolyzed to 5,7-dibromo-1-methylisatin (**11b**).[7] The β-phenylhydrazones obtained from **10a** and **10b** are identical with those obtained from **11a**[8] and **11b**, respectively.



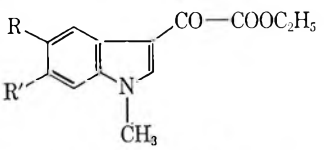
10a, R = H
b, R = Br

11a, R = H
b, R = Br

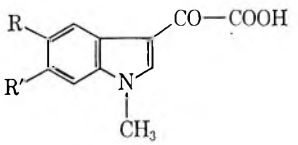
12a, R = Br; R′ = H
b, R = H; R′ = Br
c, R = R′ = Br



13a, R = Br; R′ = H
b, R = H; R′ = Br
c, R = R′ = Br



14a, R = Br; R′ = H
b, R = H; R′ = Br
c, R = R′ = Br



15a, R = Br; R′ = H
b, R = H; R′ = Br
c, R = R′ = Br

Several attempts to brominate 1-methylindole-3-carboxaldehyde (**2**) in acetic anhydride, or in carbon tetrachloride with different mole ratios of indole to bromine, were unsuccessful. When the reaction was carried out in acetic acid with a 1:1.5 mol ratio of substrate to bromine, the unreacted aldehyde was partly recovered together with a mixture of mono- and polybrominated products, whereas with excess bromine (1:3 mol) 5-bromo-1-methylindole-3-carboxaldehyde (**12a**)[9] (16.7% yield, also obtained by methylation of **13a**[2]), 2,3,5,6-tetrabromo-1-methylindole (**4a**) (26.7% yield), and a small amount (6.2%) of 3,3,5-tribromo-1-methyloxindole (**10a**) were isolated.

Displacements of formyl, acetyl, or carboxylic groups, similar to the one giving **4a** from **2**, have been already reported in indole chemistry.[1a,2,10]

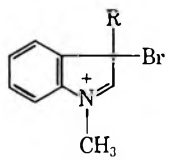
An attempt to brominate ethyl 1-methylindole-3-glyoxylate (**3**) with bromine in acetic acid did not give satisfactory results, because mostly amorphous material was obtained. On the other hand, when the reaction with bromine was carried out in acetic anhydride, substitution products were isolated in fairly good yields. Reaction of **3** with an about equimolar amount of bromine gave, in 94% yield, a product whose melting point remained unchanged through several crystallizations. This material was identified as a constant-melting mixture of 5- and 6-bromo-1-methylindole-3-glyoxylate (**14a** and **14b**). Similar constant-melting mixtures of isomeric bromoindoles have been already described[2] and, in one case, were erroneously considered as a single compound.[11,12] Saponification of the mixture of **14a** and **14b** led to an analogous mixture of the corresponding acids **15a** and **15b**; subsequent decarboxylation with copper chromite in quinoline gave a mixture of 5- and 6-bromo-1-methylindole-3-carboxaldehyde (**12a**[9] and **12b**) in an about 7:3 ratio; fractional crystallization of this mixture from benzene–petroleum ether (bp 60–80°) gave in low yield the two pure compounds **12a** and **12b**. Therefore, 5-bromo derivative **14a** is the main product of the reaction of **3** with bromine in acetic anhydride. Several attempts to separate the components **14a** and **14b** and **15a** and **15b** of the two constant-melting mixtures both by column chromatography and by fractional crystallization were unsuccessful. 6-Bromo-1-methylindole-3-carboxaldehyde (**12b**) was also obtained by methylation of **13b**.[2]

Bromination of ethyl 1-methylindole-3-glyoxylate (**3**) with bromine (1:2.5 mol) in acetic anhydride led to a mixture of **14a**, **14b**, and ethyl 5,6-dibromo-1-methylindole-3-glyoxylate (**14c**); when a larger excess of bromine (1:4 mol) was used, practically pure **14c** (95% yield) was isolated. Compound **14c** was also obtained, in 96% yield, by bromination of the mixture of **14a** and **14b**. Structure **14c** has been proved by hydrolysis to the acid **15c** and decarboxylation of the latter to 5,6-dibromo-1-methylindole-3-carboxaldehyde (**12c**), a compound also obtained by methylation of 5,6-dibromoindole-3-carboxaldehyde (**13c**).[2]

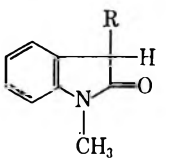
(6) W. Borsche and W. Jacobs, *Ber.*, **47**, 363 (1914).
(7) R. Pummerer and F. Meininger, *Justus Liebigs Ann. Chem.*, **590**, 189 (1954).
(8) J. Martinet, *Ann. Chim.* (Paris), **11**, 85 (1919); *Chem. Zentralbl.*, **III**, 569, (1919).
(9) W. E. Noland and C. Reich, *J. Org. Chem.*, **32**, 828 (1967).
(10) W. E. Noland and K. R. Rush, *ibid.*, **31**, 70 (1966).
(11) R. Majima and M. Kotake, *Ber.*, **63**, 2237 (1930).
(12) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **38**, 1467 (1960).

When the results of the bromination of 1-methylindole-3-carboxaldehyde and ethyl 1-methylindole-3-glyoxylate are compared with the results of the bromination of the unmethylated analogs,[2] it can be seen that N-methylindoles give better yields of bromo derivatives. In fact, indole-3-carboxaldehyde gives the 5-, 6-, and 5,6-dibromo derivatives in only very low yields (6, 3, and 5%, respectively), and ethyl indole-3-glyoxylate gives the 5,6-dibromo derivative in 82% yield.[2] Evidently, the nitrogen methylation stabilizes the indole ring and reduces the formation of tarry materials.

An interesting aspect of these reactions is the formation of dimer **6a** and of oxindoles together with simple substitution products. It is known that, in the reactions of indoles with halogenating agents, oxidation and substitution are competitive reactions.[3,13] In fact, according to Hinman and Bauman,[3b] although aqueous acetic acid favors oxidation and anhydrous acetic acid bromination, neither one is completely excluded; either of these reactions takes place *via* the same ionic intermediate **16**, which can be converted both into a 2- or 3-bromoindole derivative and into an oxindole **17**; as the second step, further bromination of



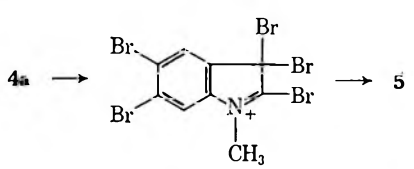
16



17

the previously formed oxindole would take place. Furthermore, and the present paper supports it (see the synthesis of compound **10b** described in the Experimental Section), it has been shown that, when oxindoles are brominated, bromine attacks only positions 3, 5, and 7.[14]

If oxindoles are intermediates in the formation of bromooxindoles, we cannot therefore explain the formation of oxindole **5** (brominated in position 6) from the corresponding oxindole **17** (R = H). On the other hand, the formation of bromooxindoles by hydrolysis of previously formed α-brominated tri- or tetrabromoindoles is very unlikely, because, when a bromine atom substitutes the benzene ring, hydrolysis of α-bromoindoles requires very drastic conditions.[3b] An attempt at hydrolysis of 2,3,5,6-tetrabromo-1-methylindole (**4a**) both by refluxing it for 5 hr with a 1:1 mixture of 3 *N* sulfuric acid and dioxane, and by storing it at room temperature for 2 days with a 1:3 mixture of concentrated hydrogen bromide and acetic acid, resulted in the complete recovery of the starting material. A possible, even if purely hypothetical, route to explain the formation of oxindole **5** could be the following one.



The hypothetical intermediate **16** rationalizes very well the formation of the dimer **6a**; probably the dimer **6b** is formed by attack of **16** on a molecule of 1-methylindole (**1**), according to the mechanism proposed by Kunori;[4] successively **6b** is brominated. This dimerization is similar to the formation of indole and skatole dimers under acidic conditions, where a proton rather than a bromonium ion initiates the process.[15] We hope that work now in progress will shed more light on these problems.

Experimental Section[16]

Brominations of 1-Methylindole (1). A. 2,3,5,6-Tetrabromo-1-methylindole (4a) and 3,3,5,6-Tetrabromo-1-methyloxindole (5).—To an ice-cold solution of 1 g (7.63 mmol) of **1** in 6 ml of acetic acid was added dropwise with stirring a solution of 6.1 g (38.0 mmol) of bromine in 6 ml of acetic acid. Stirring was continued for 2 hr at room temperature. The precipitate was collected, suspended in a 3% solution of sodium thiosulfate, again collected, and washed with water to give 2.5 g of crude **4a**. Compound **4a** was purified by dissolving it in 500–600 ml of benzene and passing the resulting solution through a column of neutral alumina (grade I, 1.5 × 25 cm). Elution with benzene gave 1.8 g (53%) of practically pure **4a**. An analytical sample, colorless crystals, mp 168–170°, was obtained by crystallization from petroleum ether (bp 60–80°).

Anal. Calcd for $C_9H_5Br_4N$: C, 24.16; H, 1.12; Br, 71.59. Found: C, 24.46; H, 1.42; Br, 71.41.

The acetic mother liquor was diluted with water; after storage for 12 hr at room temperature, the precipitate was collected, washed with water, and dried to give 0.6 g of a product that was dissolved in benzene and passed through a column of silica gel (1.5 × 25 cm). Elution with 1:1 benzene–petroleum ether (bp 60–80°) mixture gave some fractions containing a product that, after crystallization from acetic acid, yielded 0.3 g (8.5%) of **5** as light yellow plates, darkening above 220° with slow decomposition; the ir spectrum showed a strong band at *ca.* 1735 cm^{-1} (C=O).

Anal. Calcd for $C_9H_5Br_4NO$: C, 23.40; H, 1.08; Br, 69.20. Found: C, 23.60; H, 1.10; Br, 69.40.

B. 2′,3,5,5′,6,6′-Hexabromo-1,1′dimethyl-2,3′-diindolyl (6a) and 3,3,5,6-Tetrabromo-1-methyloxindole (5).—The bromination of 1 (0.5 g, 3.82 mmol) was carried out as described in A above, except that bromine (3.05 g, 19.0 mmol) was added at room temperature. Benzene eluted 0.6 g (42.8%) of practically pure **6a** as the only solid compound. The pure compound, white crystals darkening above 260° without melting, was obtained after crystallization from DMSO, mol wt 733.7 (calcd for $C_{18}H_{10}Br_6N_2$, 750; Rast method).

Anal. Calcd for $C_{18}H_{10}Br_6N_2$: C, 29.42; H, 1.36; Br, 65.30. Found: C, 29.20; H, 1.38; Br, 64.90.

Also in this case, from the acetic mother liquor, 0.15 g (8.5%) of **5** was obtained.

2,3,5,6-Tetrabromo-1-methylindole (4a) by Methylation of 2,3,5,6-Tetrabromoindole (4b).—To a suspension of 0.04 g of **4b**[2] in 2 ml of 2 *N* aqueous sodium hydroxide, 0.1 ml of dimethyl sulfate was added with stirring. Stirring was continued for 10 hr while small amounts of 2 *N* aqueous sodium hydroxide and of dimethyl sulfate were again added at intervals. The precipitate was collected, washed with water, and dried to yield 0.04 g (96.8%) of practically pure **4a**.

3,4-Dibromo-N-methyl-N-tosylaniline (8b).—To a well-stirred suspension of 8.1 g (32.2 mmol) of 3,4-dibromoaniline in 160 ml of 2 *N* aqueous sodium hydroxide was added in small portions 9.6 g (50.3 mmol) of *p*-toluenesulfonyl chloride. Stirring was continued for 4 hr at room temperature. The precipitate was collected, suspended in concentrated hydrochloric acid, again collected, and washed with water to yield 10.7 g (82%) of the tosyl derivative **8c**, mp 120–125°. To a solution of 5.0 g of **8c**

(13) J. C. Powers, *J. Org. Chem.*, **31**, 2627 (1966).

(14) (a) R. Stollé, R. Bergdoll, M. Luther, A. Auerhahn, and W. Wacker, *J. Prakt. Chem.*, **128**, 1 (1930); (b) W. C. Sumpter, M. Miller, and L. N. Hendrick, *J. Amer. Chem. Soc.*, **67**, 1656 (1945).

(15) R. L. Hinman and E. R. Shull, *J. Org. Chem.*, **26**, 2339 (1961); G. F. Smith and A. E. Walters, *J. Chem. Soc.*, 940 (1961); B. Berti, A. Da Settimo, and D. Segnini, *Ann. Chim.* (Rome), **52**, 535 (1962).

(16) Melting points are uncorrected. Ir spectra were obtained on a Perkin-Elmer Infracord 137, in Nujol mulls. Commercial acetic acid (*ca.* 98%) used in the brominations was not previously dried; acetic anhydride was freshly distilled. Comparisons between compounds were made on the basis of their infrared spectra. $MgSO_4$ was used as the drying agent, unless stated otherwise.

in a mixture of 25 ml of ethanol and 25 ml of 2 *N* aqueous sodium hydroxide was added dropwise with stirring an excess of dimethyl sulfate. Compound **8b** started to precipitate and was filtered off at intervals, while stirring was continued and small amounts of 2 *N* aqueous sodium hydroxide and of dimethyl sulfate were again added over a period of 6 hr. The collected precipitates were washed with water and dried to give 3.0 g (58%) of the pure compound **8b**, mp 78–80°. An analytical sample was obtained by crystallization from ethanol.

Anal. Calcd for $C_{14}H_{13}Br_2NO_2S$: C, 40.11; H, 3.12; Br, 38.13; S, 7.65. Found: C, 40.23; H, 3.04; Br, 37.87; S, 7.96.

5,6-Dibromo-1-methylisatin (7). A. By Synthesis.—A mixture of 6.32 g of 3,4-dibromo-N-methyl-N-tosylaniline (**8b**) and 65 ml of 75% sulfuric acid was heated at 100° for 1 hr. After cooling, the mixture was poured into crushed ice, made alkaline with 20% aqueous sodium hydroxide, and extracted with ether; the extract was washed with water, dried, and evaporated. The residual brown oil consisted of 3.0 g (75%) of **3,4-dibromo-N-methylaniline** (**8a**) and was directly used for the synthesis of **7**.

To an ice-cold suspension of 3.0 g (11.3 mmol) of **8a** in 150 ml of anhydrous carbon disulfide was added with stirring 2.87 g (22.6 mmol) of oxalyl chloride. Stirring was continued for 30 min and then the mixture was treated with 5 g of anhydrous aluminum chloride, while being stirred and refluxed for 3 hr. After cooling, the mixture was treated with crushed ice to give 1.45 g (40%) of a red precipitate, which consisted of a mixture of **7** and, probably, of 4,5-dibromo-1-methylisatin. The organic layer was separated, and the aqueous layer was extracted with ether; the combined organic extracts were washed with water, dried, and evaporated to yield 0.1 g of the same mixture of isomeric dibromoisatins (total yield 43%). Fractional crystallization from methanol of the combined mixtures yielded, as the first fraction, 0.52 g (14.4%) of **7**. An analytical sample, red crystals, mp 255–256°, was obtained by crystallization from benzene; the ir spectrum of **7** showed two strong bands at *ca.* 1735 (C=O) and 1600 cm^{-1} (C=O) and lacked the band at *ca.* 824 cm^{-1}, observed in the spectrum of the mixture of the two dibromoisatins.

Anal. Calcd for $C_9H_5Br_2NO_2$: C, 33.88; H, 1.58; N, 4.39; Br, 50.10. Found: C, 33.79; H, 1.80; N, 4.39; Br, 49.92.

B. From 3,3,5,6-Tetrabromo-1-methyloxindole (5).—A mixture of 0.1 g of **5**, 2 ml of 2 *N* aqueous sodium hydroxide, 4 ml of water, and 5 ml of ethanol was refluxed for 1 hr. Ethanol was evaporated and the residual aqueous solution was acidified with concentrated hydrochloric acid; a precipitate formed that consisted of 0.025 g (36.2%) of practically pure **7**.

C. By Oxidation of 6a.—A suspension of 0.2 g of **6a** in a mixture of 4 ml of acetic acid and 1 ml of water was treated with 0.3 g of chromic anhydride and heated at 100° for 30 min; 0.25 g of chromic anhydride was again added; and the suspension was heated at 100° for an additional 30 min. After cooling, the mixture was poured into 200 ml of water and extracted with three 100-ml portions of benzene. The combined extracts were washed with water, dried, and concentrated to give 0.050 g (28.7%) of practically pure **7**.

5,6-Dibromo-1-methylisatin-β-phenylhydrazone. A. From 5,6-Dibromo-1-methylisatin (7).—A mixture of 0.04 g of **7**, 5 ml of ethanol, and three drops of acetic acid was treated with phenylhydrazine in slight excess and refluxed for 1 hr. Upon cooling, a precipitate formed, which was collected and washed with ethanol to give 0.045 g (88%) of the β-phenylhydrazone; an analytical sample, orange needles, mp 220–222°, was obtained after crystallization from acetic acid.

Anal. Calcd for $C_{15}H_{11}Br_2N_3O$: N, 10.3; Br, 39.1. Found: N, 10.5; Br, 39.3.

B. From 3,3,5,6-Tetrabromo-1-methyloxindole (5).—When 0.1 g of **5** was treated exactly as described in A, 0.06 g (67.7%) of the same β-phenylhydrazone was obtained.

4,5-Dibromo-N-methylanthranilic acid (9a). A. By Methylation of 4,5-Dibromoanthranilic acid (9b).—When 0.2 g of **9b**[2] was treated as described for 2,3,5,6-tetrabromoindole (**4b**), except that the mixture was stirred for 24 hr, a precipitate formed, which dissolved almost completely when the reaction mixture was heated on a steam bath; a small amount of undissolved amorphous material was eliminated by filtration. The filtrate was cautiously acidified with 2 *N* hydrochloric acid; a precipitate formed which was collected, washed with water, and dried to yield 0.08 g (38%) of **9a**. An analytical sample was obtained after two sublimations at 220° (3 mm). The pure compound, light yellow needles, melted at 258–260° (fast heating); on slow heating, the compound volatilized without melting. The ir spectrum showed bands at *ca.* 3360 (NH) and *ca.* 1670 cm^{-1} (C=O).

Anal. Calcd for $C_8H_7Br_2NO_2$: C, 31.06; H, 2.27; Br, 51.80. Found: C, 31.00; H, 2.39; Br, 51.50.

B. By Oxidation of 5,6-Dibromo-1-methylisatin (7).—A suspension of 0.1 g of **7** in a mixture of 5 ml of 2 *N* aqueous sodium hydroxide and 3 ml of water was treated with 3 ml of 36% hydrogen peroxide, heated at 100° for 1 hr, and stored at room temperature for 2 days. The mixture was cautiously acidified with 2 *N* hydrochloric acid; a precipitate formed which was collected, washed with water, and dried to yield 0.025 g (25.8%) of **9a**.

C. By Oxidation of 3,3,5,6-Tetrabromo-1-methyloxindole (5).—A suspension of 0.3 g of **5** in a mixture of 8 ml of 2 *N* aqueous sodium hydroxide and 5 ml of water, was treated with 3 ml of 36% hydrogen peroxide and heated at 100° for 2 hr. After cooling, the undissolved material was collected and washed with water; 0.13 g of the starting material was recovered. The combined filtrates were acidified with 2 *N* hydrochloric acid to give 0.05 g (44.2%, based on unrecovered starting material) of **9a**.

1,1′-Dimethyl-2,3′-diindolyl (6b).—To an ice-cold, stirred solution of 0.464 g (2.0 mmol) of 2,3′-diindolyl[5] in 20 ml of dry DMF, was added, under nitrogen, 0.2 g (41.6 mmol) of a 50% suspension of sodium hydride in mineral oil. The mixture was allowed to warm to 25° and stand for 2 hr, while being stirred. It was then cooled in an ice bath and treated with a solution of 0.68 g (48.0 mmol) of methyl iodide in 12 ml of dry ether. The resulting solution was left for 18 hr under nitrogen at 25°, concentrated under reduced pressure to about 10 ml, and poured into water. A precipitate formed which was collected, washed with water, and dried to give 0.52 g (100%) of **6b**, mp 133–135° (lit.[4] mp 134–135°), identical with an authentic sample prepared according to Kunori by treating 1-methylindole (**1**) with dioxane–bromine complex in THF solution.[4]

The compound gave a positive Ehrlich test, and its chromic oxidation, carried out as described for the conversion of **6a** into **7**, gave, as a single compound, 1-methylisatin, mp 134° (lit.[17] mp 134°).

Compound 6a by Bromination of 6b.—To a well-stirred suspension of 0.5 g (1.92 mmol) of **6b** in 5 ml of acetic acid, 2 ml of acetic acid containing 2.49 g (15.5 mmol) of bromine was added dropwise at room temperature. Stirring was continued for 5 hr at room temperature. The precipitate was collected, washed with acetic acid, dried, and crystallized from DMSO to give 1.1 g (78%) of practically pure **6a**.

3,3,5-Tribromo-1-methyloxindole (10a). A. By Bromination of 1-Methyloxindole.—A solution of 0.3 g (2.04 mmol) of 1-methyloxindole in 25 ml of dry carbon tetrachloride was treated with 2.0 g (12.5 mmol) of bromine and refluxed until the evolution of hydrogen bromide ceased (*ca.* 6 hr). The resulting solution was concentrated to about 6 ml; on cooling, a precipitate formed which was collected and washed with carbon tetrachloride to give 0.55 g (70%) of practically pure **10a**. An analytical sample, pale yellow prisms, mp 171–173°, was obtained after crystallization from acetic acid; the ir spectrum showed a strong band at *ca.* 1730 cm^{-1} (C=O).

Anal. Calcd for $C_9H_6Br_3NO$: C, 28.20; H, 1.56; Br, 62.50. Found: C, 28.48; H, 1.68; Br, 62.20.

The hydrolysis of **10a**, carried out according to Stollé,[14a] with a mixture of ethanol and 2 *N* aqueous sodium hydroxide, gave 5-bromo-1-methylisatin (**11a**), mp 172–173° (lit.[6] mp 172–173°).

The β-phenylhydrazone obtained from **10a** was identical with an authentic sample prepared from **11a** and melted at 170–172° (lit.[8] mp 164°).

B. By Bromination of 5-Bromo-1-methyloxindole.—Practically pure **10a** was also obtained in 95% yield, when 5-bromo-1-methyloxindole[14a] was brominated exactly as described in A.

3,3,5,7-Tetrabromo-1-methyloxindole (10b). A. By Bromination of 1-Methyloxindole.—A solution of 10 g (62.5 mmol) of bromine in 30 ml of water containing 15 g of potassium bromide was added to a boiling solution of 2.0 g (13.6 mmol) of 1-methyloxindole in 200 ml of water. The mixture was allowed to cool at room temperature and stand for 1 night. The precipitate was collected, washed with water, dried, dissolved in 250 ml of carbon tetrachloride, and treated with excess bromine. The resulting solution was refluxed until the evolution of hydrogen bromide ceased (*ca.* 15 hr), and then was concentrated; 5.5 g (87.4%) of practically pure **10b** crystallized on cooling. An analytical sample, pale yellow needles, mp 227–230°, was crys-

(17) E. Fischer and O. Hess, *Ber.*, **17**, 565 (1884).

tallized from acetic acid; the ir spectrum showed a strong band at *ca.* 1725 cm^{-1} (C=O).

Anal. Calcd for $C_9H_5Br_4NO$: C, 23.40; H, 1.08; Br, 69.20. Found: C, 23.70; H, 1.20; Br, 68.90.

The hydrolysis of **10b**, carried out according to Stollé[14a] with a mixture of ethanol and 2 *N* aqueous sodium hydroxide, gave 5,7-dibromo-1-methylisatin (**11b**), mp 182–183° (lit.[7] mp 182–183°).

B. By Bromination of 3,3,5-Tribromo-1-methyloxindole (10a).—A solution of 1.67 g (10.4 mmol) of bromine in 10 ml of water containing 3 g of potassium bromide was added to a boiling solution of 1.0 g (2.60 mmol) of **10a** in 300 ml of 10% aqueous acetic acid. After storage at room temperature for 1 night, a precipitate was collected, washed with water, and crystallized from acetic acid to give 1.0 g (83%) of pure **10b**.

5,7-Dibromo-1-methylisatin-β-phenylhydrazone.—A mixture of 0.2 g of **10b**, 10 ml of ethanol, and 0.2 ml of acetic acid was treated with excess phenylhydrazine and refluxed for 2 hr. Ethanol was evaporated; the phenylhydrazone, orange needles, crystallized on cooling (80% yield). An analytical sample, mp 200–201.5°, was crystallized from acetic acid.

Anal. Calcd for $C_{15}H_{11}Br_2N_3O$: C, 44.03; H, 2.69; Br, 39.10. Found: C, 44.39; H, 2.68; Br, 38.86.

The same phenylhydrazone was obtained by a similar treatment of 5,7-dibromo-1-methylisatin (**11b**).

Bromination of 1-Methylindole-3-carboxaldehyde (2). 5-Bromo-1-methylindole-3-carboxaldehyde (12a), 2,3,5,6-Tetrabromo-1-methylindole (4a), and 3,3,5-Tribromo-1-methyloxindole (10a).—To a solution of 0.2 g (1.26 mmol) of **2** in 2.5 ml of acetic acid, 2 ml of acetic acid containing 0.605 g (3.78 mmol) of bromine was added dropwise with stirring. Stirring was continued for 1 hr at room temperature. A precipitate formed which was collected, washed with acetic acid, and suspended in a 3% solution of sodium thiosulfate; the resulting compound was again collected, washed with water, and dried to give 0.05 g (16.7%) of practically pure **12a**. An analytical sample, colorless needles, mp 137–138° (lit.[9] mp 138°), was crystallized from methanol; the ir spectrum showed a band at *ca.* 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_8BrNO$: C, 50.44; H, 3.39; Br, 33.60. Found: C, 50.74; H, 3.28; Br, 33.38.

The acetic mother liquor separated, after storage at room temperature for one night, 0.15 g (26.7%) of **4a**, and then was diluted with water; a precipitate was collected and crystallized from acetic acid (charcoal) to give 0.03 g (6.2%) of **10a**.

5-Bromo-1-methylindole-3-carboxaldehyde (12a) by Methylation of 5-Bromoindole-3-carboxaldehyde (13a).—Compound **12a** was obtained in 91.7% yield from 0.2 g of **13a**[2] as described for the methylation of 2,3,5,6-tetrabromoindole (**4b**), except that the mixture was stirred for 20 hr.

Ethyl 1-Methylindole-3-glyoxylate (3).—A solution of 6.0 g (45.8 mmol) of 1-methylindole (**1**) in 100 ml of dry ether was treated dropwise at 0°, while being stirred, with 11.2 g (88.2 mmol) of oxalyl chloride. 1-Methylindole-3-glyoxalyl chloride was rapidly formed as orange crystals. Stirring was continued for 45 min at room temperature; the chloride was then collected, washed with ether (8.8 g, mp 116–117°), and treated with 20 ml of dry ethanol. After 15 hr of storage at room temperature, 8.0 g (75.7%) of **3** was collected. An analytical sample was obtained after two crystallizations from ethanol, mp 90–91°; the ir spectrum showed bands at *ca.* 1720 (C=O) and *ca.* 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.81; H, 5.78; N, 5.94.

Brominations of Ethyl 1-Methylindole-3-glyoxylate (3). A. Constant-Melting Mixture of 5- and 6-Bromo-1-methylindole-3-glyoxylate (14a and 14b).—To a solution of 0.5 g (2.16 mmol) of **3** in 2 ml of acetic anhydride was added dropwise with stirring a solution of 0.416 g (2.60 mmol) of bromine in 1 ml of acetic anhydride. The mixture was left at room temperature for 5 hr and then poured into crushed ice; the precipitate which formed was collected and washed with water to give 0.63 g (94%) of a mixture of **14a** and **14b**, which was crystallized twice from ethanol to yield colorless needles, mp 114–116° (the melting point remained unchanged through several crystallizations); the ir spectrum showed bands at *ca.* 1740 (C=O) and *ca.* 1640 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{12}BrNO_3$: C, 50.32; H, 3.87; Br, 25.80. Found: C, 50.09; H, 3.86; Br, 25.97.

All attempts to separate the components of such mixture both by column chromatography and by fractional crystallization were unsuccessful.

B. Ethyl 5,6-Dibromo-1-methylindole-3-glyoxylate (14c).—When 1.0 g (4.32 mmol) of **3** was treated with 2.77 g (17.3 mmol) of bromine exactly as described in A, 1.6 g (95%) of **14c** was obtained. Purification by crystallization from ethanol gave an analytical sample, colorless needles, mp 129–130°. The ir spectrum showed bands at *ca.* 1725 (C=O) and *ca.* 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{11}Br_2NO_3$: C, 40.10; H, 2.83; Br, 41.15. Found: C, 40.29; H, 2.81; Br, 41.05.

When the constant melting mixture of **14a** and **14b** was treated with bromine (1:2 mol ratio) in acetic anhydride and worked up exactly as described above, compound **14c** was obtained in 96% yield.

Constant-Melting Mixture of 5- and 6-Bromo-1-methylindole-3-carboxylic Acid (15a and 15b).—A suspension of 0.37 g of the mixture of **14a** and **14b** in 10 ml of 2 *N* aqueous sodium hydroxide was heated at 100° for 2 hr. Acidification of the alkaline solution with concentrated hydrochloric acid gave 0.3 g (89%) of a mixture of **15a** and **15b**, which, after crystallization from methanol, melted at 238–240° (the melting point remained unchanged through several crystallizations); the ir spectrum showed bands at *ca* 3300 (OH), *ca.* 1755 (C=O), and *ca.* 1625 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_8BrNO_3$: Br, 28.40. Found: Br, 28.63.

All attempts to separate the components of such mixture both by column chromatography and by fractional crystallization were unsuccessful.

Decarboxylation of the Constant-Melting Mixture of 15a and 15b. 5- and 6-Bromo-1-methylindole-3-carboxaldehyde (12a and 12b).—Two grams of the mixture of **15a** and **15b**, 6 ml of quinoline, and a catalytic amount of copper chromite were heated at 235–240° until the evolution of carbon dioxide ceased. After cooling the mixture was poured in 2 *N* hydrochloric acid; a precipitate formed which was collected, washed, dried, and extracted repeatedly with hot benzene; the combined extracts (charcoal) were washed with 2 *N* aqueous sodium carbonate, dried, and concentrated on steam bath. Acidification of the alkaline extract with 2 *N* hydrochloric acid gave 0.5 g of the starting mixture of the acids **15a** and **15b**. Fractional dilution of the benzene solution with petroleum ether (bp 60–80°) yielded first compound **12a**[9] (0.03 g after crystallization from methanol, 2.36% based on unrecovered starting material) and then 0.22 g (17.3% based on unrecovered starting material) of a mixture of **12a** and **12b** (its ir spectrum was identical with the spectrum of an artificial mixture containing **12a** and **12b** in 7:3 ratio); the last fractions contained 0.013 g (1.05% based on unrecovered starting material) of practically pure **12b**. An analytical sample of **12b**, white crystals, mp 150–151°, was obtained by crystallization from benzene; the ir spectrum showed a strong band at *ca.* 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_8BrNO$: C, 50.44; H, 3.39; Br, 33.60. Found: C, 50.80; H, 3.45; Br, 33.41.

6-Bromo-1-methylindole-3-carboxaldehyde (12b) by Methylation of 6-Bromoindole-3-carboxaldehyde (13b).—Compound **12b** was obtained in 88% yield from 0.07 g of **13b**[2] as described for the methylation of 5-bromoindole-3-carboxaldehyde (**13a**) except that the mixture was stirred for 40 hr.

5,6-Dibromo-1-methylindole-3-glyoxylic Acid (15c).—A suspension of 0.32 g of **14c** in 10 ml of 2 *N* aqueous sodium hydroxide was heated at 100° for 2 hr. Acidification of the alkaline solution with concentrated hydrochloric acid gave 0.28 g (94.5%) of **15c**. An analytical sample was crystallized from an acetone–methanol mixture to give light yellow plates, mp 251–253° dec. The ir spectrum showed bands at *ca.* 3300 (OH), *ca.* 1770 (C=O), and *ca.* 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_7Br_2NO_3$: C, 36.60; H, 1.93; Br, 44.30. Found: C, 36.85; H, 1.87; Br, 44.05.

5,6-Dibromo-1-methylindole-3-carboxaldehyde (12c). A. By Decarboxylation of Acid 15c.—The decarboxylation of 0.2 g of **15c** was carried out as described for the mixture of **14a** and **14b**. The washed and dried benzene extract (charcoal) was concentrated and diluted with petroleum ether (bp 30–50°); the solution slowly separated 0.04 g (22.8%) of **12c**. The compound was crystallized from benzene to give light yellow prisms, mp 209–211°; the ir spectrum showed a strong band at *ca.* 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_7Br_2NO$: C, 37.89; H, 2.21; Br, 50.45. Found: C, 38.16; H, 2.26; Br, 50.20.

B. By Methylation of 5,6-Dibromoindole-3-carboxaldehyde

(**13c**).—The methylation of 0.2 g of **13c**,[2] carried cut as described for 5-bromoindole-3-carboxaldehyde (**13a**), gave 0.185 g (88.5%) of **12c**.

Registry No.—Bromine, 7726-95-6; **3**, 25055-54-3; **4a**, 25055-55-4; **5**, 25055-56-5; **6a**, 25055-57-6; **7**, 25055-58-7; **7** (phenylhydrazone), 25055-59-8; **8b**, 25055-60-1; **9a**, 25055-61-2; **10a**, 25055-62-3; **10b**, 25055-63-4; **10b** (phenylhydrazone), 25055-64-5; **12b**, 25055-65-6; **12c**, 25055-66-7; **14a**, 25055-67-8; **14b**, 25055-68-9; **14c**, 25055-50-9; **15a**, 25055-51-0; **15b**, 25055-52-1; **15c**, 25055-53-2.

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Alkyl Nitrate Nitration of Active Methylene Compounds. VIII. Synthesis of α-Nitrosulfonate Esters

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The alkyl nitrate nitration of neopentyl sulfonate esters gives the corresponding neopentyl α-nitrosulfonate esters in good yield. On the other hand, the nitration of ethyl sulfonate esters such as ethyl 1-butanesulfonate (**1a**) leads not only to ethyl 1-nitro-1-butanesulfonate (**2a**) but also to potassium 1-nitro-1-butanesulfonate (**3**). Compound **3** arises from a β-elimination reaction on the ester portion of the molecule which occurs during the nitration step and not during anion formation or during the acidification step.

In continuation of our studies of the alkyl nitrate nitration,[1] we are now reporting on its application to the preparation of α-nitrosulfonate esters which constitute a new class of compounds.

In preliminary experiments it was established that nitration of ethyl 1-butanesulfonate (**1a**) gave best results in the potassium amide–liquid ammonia system, affording a 54.8% yield of ethyl 1-nitro-1-butanesulfonate (**2a**). The yield of **2a** was only 35.5 and 37.0%, respectively, when nitrations were performed in sodium amide–liquid ammonia and potassium *t*-butoxide–THF. In addition to **2a**, potassium 1-nitro-1-butanesulfonate (**3**) was also obtained in each of the base-solvent systems employed (eq 1). However, only neopentyl α-nitrobutanesulfonate (**2b**) was obtained from the nitration of neopentyl butanesulfonate (**1b**).

$$\underset{\mathbf{1}}{H_3C(CH_2)_3SO_3R} \xrightarrow[2.\ H^+]{1.\ KNH_2\text{–liquid } NH_3\text{–}R^1ONO_2}$$

$$\underset{\mathbf{2}}{H_3C(CH_2)_2CH(NO_2)SO_3R} + \underset{\mathbf{3}}{H_3C(CH_2)_2CH(NO_2)SO_3^-K^+} + \underset{\mathbf{12}}{CH_2{=}CH(CH_2)_5CH_3} \quad (1)$$

a, R = CH_2CH_3; **b**, R = $CH_2C(CH_3)_3$; **c**, R = $(CH_2)_7CH_3$; R^1 = C_2H_5 or n-C_3H_7

The acid salt rather than the nitronate structure was assigned to compound **3** on the basis of its nmr spectrum which showed the characteristic methine proton absorption at 5.48–5.72 ppm.

The results of the nitration of various neopentyl sulfonate estera are summarized in Table I. It is noteworthy that in order to obtain optimum yields of α-nitrosulfonate esters containing 8–12 carbons in the side chain, more concentrated reaction mixtures had to be employed, (instead of 250 ml, only 100 ml of liquid ammonia was used). In the case of neopentyl 1-hexadecanesulfonate (**4**), no nitrated product was obtained. Even though anion formation was carried out with potassium amide in THF at 65°, 95% of the ester **4** was recovered. The failure of **4** to undergo nitration was due to the fact that it was not converted to its anion. This was ascertained from a deuterium-exchange experiment, for nmr and mass spectral data showed that no deuterium was incorporated into **4** after treatment with potassium amide in liquid ammonia and subsequent acidification with deuterium oxide in anhydrous ether.[2] Under similar reaction conditions, deuterium was incorporated into **1b** and neopentyl 1-dodecanesulfonate to the extent of 100 and 75%, respectively.

The nitration was also successful with a disulfonate ester.

The nitration was also successful with a disulfonate ester. Thus dineopentyl 1,4-butanedisulfonate was converted into dineopentyl 1,4-dinitro-1,4-butanedisulfonate in 68.9% yield.

The neopentyl α-nitrosulfonate esters were identified by infrared and nmr spectra and by conversion to the corresponding bromo derivatives (eq 2).

$$\underset{\displaystyle NO_2}{RCHSO_3R^1} \xrightarrow[2.\ Br_2;\ CCl_4]{1.\ KOH\text{–}C_2H_5OH} \underset{\displaystyle NO_2}{\overset{\displaystyle Br}{RCSO_3R^1}} \quad (2)$$

In contrast to the results in the nitration of *t*-butyl α-methylbutyrate which led with decarboxylation to 2-nitrobutane,[1a] neopentyl 2-butanesulfonate was converted to neopentyl 2-nitro-2-butanesulfonate (**5**) in 34.7% yield. The lower yield of **5** as compared with **2b** could be caused by the methyl group in the α position, which lowers the acidity of the α hydrogen[3] and hinders the approach of base in forming the carbanion.

The nitration of ethyl 2-butanesulfonate (**6**) led in 53.1% yield to potassium 2-nitro-2-butanesulfonate (**7**) instead of the expected α-nitrosulfonate ester. In addition to **7**, 35.1% ethyl 3-methyl-3-pentanesulfonate (**8**) was also isolated (eq 3).

(1) For previous publications, see (a) H. Feuer and R. P. Monter, *J. Org. Chem.*, **34**, 991 (1969); (b) H. Feuer and J. P. Lawrence, *J. Amer. Chem. Soc.*, **91**, 1856 (1969); (c) W. E. Truce, T. C. Klinger, J. E. Paar, and by H. Feuer, and D. K. Wu, *J. Org. Chem.*, **34**, 3104 (1969).

(2) A steric factor might be responsible for preventing conversion of compound **4** to its anion. Models indicate that coiling back of the alkyl chain could hinder approach to the α hydrogen.

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, N. Y., 1959.

TABLE I

ALKYL NITRATE NITRATION OF NEOPENTYL SULFONATE ESTERS

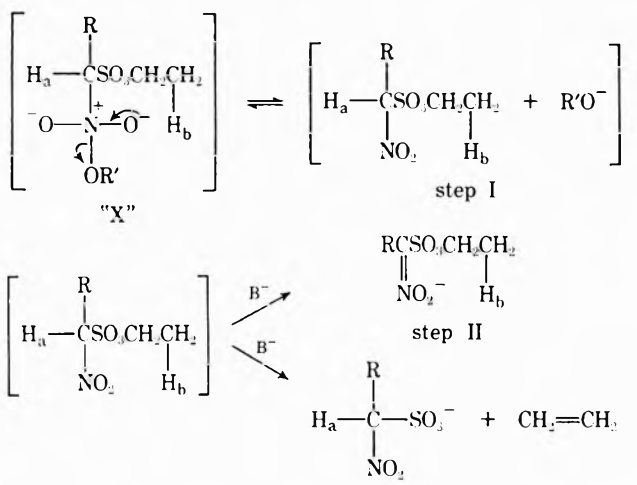
$RSO_3CH_2C(CH_3)_3$, R	Neopentyl 1-nitrosulfonate ester Yield, %[a]	Yield, %[b]
CH_3CH_2-	73.8 (22.2)[c]	
n-C_4H_9-	75.5 (22.2)	75.6 (20.2)
n-$C_6H_{13}-$	55.8 (36.7)	75.2 (20.8)
n-$C_8H_{17}-$	32.8 (61.6)	75.6 (21.7)
n-$C_{10}H_{21}-$	16.9 (78.1)	55.7 (39.7)
n-$C_{12}H_{25}-$	3.0 (93.4)	33.9[d] (62.7)
n-$C_{16}H_{33}-$	0 (95.7)	0 (95.5)
$CH_3CH_2CH(CH_3)-$		34.7 (59.8)

[a] Reactions were carried out with potassium amide in 250 ml of liquid ammonia at −33°. The nitration time was 5 min. [b] Reactions were carried out with potassium amide in 100 ml of liquid ammonia at −33°. The nitration time was 1 hr. [c] The numbers in parenthesis represent recovered starting material. [d] The yield was 47.0% when anion formation was carried out with potassium amide in THF at 65°, and the nitration at −33°.

$$H_3CCH_2CH(CH_3)SO_3CH_2CH_3 \xrightarrow[2.\ NH_4Cl]{1.\ KNH_2\text{–liquid }NH_3\text{–}R^1ONO_2} \underset{7}{H_3CCH_2\overset{\overset{NO_2}{|}}{C}(CH_3)SO_3^-K^+} + \underset{8}{(H_3CCH_2)_2\overset{\overset{CH_3}{|}}{C}SO_3CH_2CH_3} \quad (3)$$
6

It is possible that ethyl 2-nitro-2-butanesulfonate (**9**) is an intermediate in the reaction, and that it is converted by a nucleophilic attack of the anion of **6** on the ester portion of **9** to compounds **7** and **8**. However, salt **7** could also form *via* a β-elimination reaction as shown in step III of Scheme I (*vide infra*).

SCHEME I



That an intermediate such as **9** is involved in the formation of **8** was indicated by the fact that **6** was recovered unchanged in 93.4% yield when treated with potassium amide in liquid ammonia. However, it should be emphasized that the nitro group is not essential for the alkylation reaction since the reaction of **8** with neopentyl 2-butanesulfonate (**10**) in the potassium amide–liquid ammonia system led to neopentyl 3-methyl-3-pentanesulfonate (**11**) in 21.1% yield (eq 4).

$$CH_3CH_2CH(CH_3)SO_3CH_2C(CH_3)_3 + 8 \xrightarrow[2.\ NH_4Cl]{1.\ KNH_2\text{–liquid }NH_3} \underset{11}{(CH_3CH_2)_2\overset{\overset{CH_3}{|}}{C}\text{—}SO_3CH_2C(CH_3)_3} + (CH_3CH_2)_2\overset{\overset{H_3C}{|}}{C}SO_3^-K^+ \quad (4)$$
10

Study of the Elimination Reaction.—It has been suggested[4] that the alkyl nitrate nitration of an active methylene compound proceeds *via* collapse of an intermediate which is formed by nucleophilic attack of a carbanion on the alkyl nitrate. The results from the nitration of neopentyl sulfonate esters are consistent with this suggested mechanism. However, the formation of potassium 1-nitrobutanesulfonate (**3**) in the nitration of compound **1a** (eq 1) requires additional clarification. It involves a β-elimination reaction in the ester part of **1**, for the nitration of octyl 1-butanesulfonate (**1c**) gave 1-octene (**12**) in addition to **3** and octyl 1-nitro-1-butanesulfonate (**2c**). That the reaction takes place during the nitration step and not during anion formation or the acidification step is based on the results from the following control experiments. (a) Compound **1a** was recovered in 92% yield on treatment with potassium amide in liquid ammonia, followed by acidification with ammonium chloride. (b) Potassium 1-ethoxysulfonyl-1-butanenitronate was converted in 96.4% yield to ethyl 1-nitro-1-butanesulfonate (**2a**) on treatment with potassium amide in liquid ammonia and subsequent acidification with ammonium chloride. (c) Treatment of **2a** with potassium amide in liquid ammonia followed by acidification with ammonium chloride gave a mixture consisting of **3** (26.3%) and **2a** (67.3%) (eq 5). A mechanism consistent with these observations is proposed in Scheme I.

$$\underset{\overset{\overset{NO_2}{|}}{}}{CH_3(CH_2)_2CHSO_3CH_2CH_3} \xrightarrow[2.\ NH_4Cl]{1.\ KNH_2\text{–liquid }NH_3} \underset{\overset{\overset{NO_2}{|}}{}}{CH_3(CH_2)_2CHSO_3^-K^+} + \mathbf{2a} \quad (5)$$
2a 3

In step I intermediate "X" collapses into α-nitrosulfonate ester and alkoxide. According to the results of control experiment c, a competitive reaction can occur in which the base can then attack the α proton (H_a) to give the nitronate salt as shown in step II, or alternately attack the β proton (H_b) in the ester portion to give the α-nitrosulfonic acid salt and olefin (step III).

It is of interest that the nitration of carboxylic esters[1a] gave nitroalkanes which arose *via* a decarboxylation rather than an elimination reaction.

Experimental Section

All melting points are uncorrected. All infrared spectra were taken with a Perkin-Elmer recording spectrophotometer, Models 21 and 421. Nuclear magnetic resonance spectra were determined in a Varian Model A-60 analytical nmr spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph A-700 using a 4-ft SF-96 on Chromosorb W column and a 6-ft SE-30 on Chromosorb P column. Solvents were evaporated on a Buchler flash evaporator.

(4) H. Feuer and C. Savides, *J. Amer. Chem. Soc.*, **91**, 5826 (1959).

Reagents.—Ethyl and propyl nitrate and ethane and 1-butanesulfonyl chloride of Eastman White Label grade were used as received. All alkyl halides used for the preparation of the corresponding sulfonyl chlorides by methods described in the literature[5,6] were from commercial sources.

Neopentyl 1-Butanesulfonate (1b).—The following experiment is typical of the procedure employed for preparing sulfonate esters.[7] To a mixture consisting of neopentyl alcohol (30.36 g, 0.3 mol), triethylamine (30.36 g, 0.3 mol), and benzene (150 ml) was added dropwise in 1 hr 1-butanesulfonyl chloride (26.45 g, 0.3 mol) at 0–10°. Stirring for 12 hr more at 20°, filtering, and washing the filtrate with four 60-ml portions of 4% hydrochloric acid and then with three 80-ml portions of water was followed by drying (Na_2SO_4) and concentrating the benzene extract. Distillation of the residue afforded 49.55 g (79.5%) of **neopentyl 1-butanesulfonate (1b)**: bp 78–80° (0.6 mm); $n^{20}D$ 1.4339; nmr (CCl_4) δ 0.86–1.10 (t, 3, CH_3), 1.0 [s, 9 $C(CH_3)_3$], 1.32–2.08 [m, 4, $(CH_2)_2$], 2.96–3.22 (t, 2, CH_2SO_3), and 3.87 (s, 2, OCH_2).

Anal. Calcd for $C_9H_{20}O_3S$: C, 51.89; H, 9.68; S, 15.39. Found: C, 51.73; H, 9.60; S, 15.50.

By the same procedure, the following alkyl sulfonates were prepared [satisfactory analytical data (± 0.35% for C, H, and S) were reported for each product (Editor)]: octyl 1-butanesulfonate (1c), 76.3%, bp 108° (0.2 mm), $n^{20}D$ 1.4438; neopentyl 2-butanesulfonate (10), 70.5%, bp 59° (0.15 mm), $n^{20}D$ 1.4346; ethyl 2-butanesulfonate (6), 81%, bp 65° (0.2 mm), $n^{20}D$ 1.4311; neopentyl ethanesulfonate, 79.4%, bp 55° (0.12 mm), $n^{20}D$ 1.4290; neopentyl 1-hexanesulfonate, 81%, bp 86° (0.25 mm), $n^{20}D$ 1.4378; neopentyl 1-octanesulfonate, 80.9%, bp 110–112° (0.38 mm), $n^{20}D$ 1.4420; neopentyl 1-decanesulfonate, 82.2%, bp 140–141° (<0.001 mm), $n^{20}D$ 1.4458; neopentyl 1-dodecanesulfonate, 70.5%, bp 147° (<0.001 mm), $n^{20}D$ 1.4484; neopentyl 1-hexadecanesulfonate (4), 59.2%, mp 47–48° (isopropyl alcohol); dineopentyl 1,4-butanedisulfonate, 57.3%, mp 125–127° (CCl_4).

Neopentyl 1-Nitro-1-butanesulfonate (2b).—The following is typical of the procedure employed for preparing α-nitrosulfonate esters. Into an oven-dried, nitrogen-flushed, 200-ml round-bottom four-necked flask equipped with a Dry Ice condenser, thermometer, mechanical stirrer, and dropping funnel were placed freshly cut potassium (3.91 g, 0.10 g-atom) and a catalytic amount of ferric nitrate in 100 ml of anhydrous ammonia at −33°. After the potassium amide had formed, neopentyl 1-butanesulfonate (1b) (10.42 g, 0.05 mol) was added in 2 min. After stirring for 3 min longer, propyl nitrate (15.77 g, 0.15 mol) was added in 5 min[8] at −35° and stirring was continued for 55 min. The reaction mixture was then acidified with ammonium chloride (5.89 g, 0.11 mol) at −50° and the ammonia replaced with anhydrous ether. Filtering off the potassium chloride, extracting the ethereal filtrate with 10% aqueous potassium hydroxide (1b remained in the ethereal layer), reacidifying the basic extract with glacial acetic acid, extracting the aqueous acidic layer with ether, drying the combined extracts (Na_2SO_4), and concentrating *in vacuo* gave 9.6 g (75.6%) of analytically pure **2b**:[9] $n^{20}D$ 1.4451; ir (neat) 1384 and 1183 (SO_2), and 1575 and 1372 cm^{-1} (NO_2); nmr (CCl_4) δ 0.92–1.16 (t, 3, CH_3), 1.02 [s, 9, $C(CH_3)_3$], 1.25–1.70 (m, 2, CH_3CH_2), 2.2–2.62 (m, 2, CH_2CH), 4.08 (s, 2, OCH_2), and 5.52–5.77 (q, 1, CH).

Anal. Calcd for $C_9H_{19}NO_5S$: C, 42.67; H, 7.56; N, 5.53; S, 12.66. Found: C, 42.96; H, 7.54; N, 5.29; S, 12.78.

Neopentyl 1-nitro-1-ethanesulfonate (73.8%): $n^{20}D$ 1.4441; ir (neat) 1375 and 1180 (SO_2), and 1578 and 1348 cm^{-1} (NO_2); nmr (CCl_4) δ 1.03 [s, 9, $C(CH_3)_3$], 1.92–2.04 (d, 3, CH_3), 4.06 (s, 2, OCH_2), and 5.53–5.88 (q, 1, CH).

Anal. Calcd for $C_7H_{15}NO_5S$: C, 37.32; H, 6.71; N, 6.22; S, 14.24. Found: C, 37.25; H, 6.56; N, 6.22; S, 14.24.

Neopentyl 1-nitro-1-hexanesulfonate (75.2%): $n^{20}D$ 1.4470; ir (neat) 1373 and 1180 (SO_2), and 1570 and 1348 cm^{-1} (NO_2); nmr (CCl_4) δ 0.9–1.05 (t, 3, CH_3), 1.02 [s, 9, $C(CH_3)_3$], 1.3–1.5 [m, 6, $CH_3(CH_2)_3$], 2.12–2.55 (m, 2, CH_2CH), 4.07 (s, 2, OCH_2), and 5.48–5.71 (q, 1, CH).

Anal. Calcd for $C_{11}H_{23}NO_5S$: C, 46.95; H, 8.24; N, 4.98; S, 11.40. Found: C, 47.12; H, 8.13; N, 5.19; S, 11.56.

Neopentyl 1-nitro-1-octanesulfonate (75.6%): $n^{20}D$ 1.4502; ir (neat) 1378 and 1181 (SO_2), and 1572 and 1351 cm^{-1} (NO_2); nmr (CCl_4) δ 0.88–1.05 (t, 3, CH_3), 1.0 [s, 9, $C(CH_3)_3$], 1.32 [s, 10, $CH_3(CH_2)_6$], 2.18–2.46 (m, 2, CH_2CH), 3.97 (s, 2, OCH_2), and 5.36–5.60 (q, 1, CH).

Anal. Calcd for $C_{13}H_{27}NO_5S$: C, 50.46; H, 8.80; N, 4.53; S, 10.36. Found: C, 50.69; H, 8.78; N, 4.69; S, 10.35.

Neopentyl 1-nitro-1-decanesulfonate (55.7%): $n^{20}D$ 1.4552; ir (neat) 1384 and 1180 (SO_2), and 1575 and 1368 cm^{-1} (NO_2); nmr (CCl_4) δ 0.88–1.05 (t, 3, CH_3), 0.99 [s, 9, $C(CH_3)_3$], 1.28 [s, 14, $CH_3(CH_2)_7$], 2.0–2.4 (m, 2, CH_2CH), 3.98 (s, 2, OCH_2), and 5.34–5.58 (q, 1, CH).

Anal. Calcd for $C_{15}H_{31}NO_5S$: C, 53.38; H, 9.26; N, 4.15; S, 9.50. Found: C, 53.47; H, 9.55; N, 3.91; S, 9.69.

Neopentyl 1-Nitro-1-dodecanesulfonate.—The general procedure was followed except anion formation was performed at 65° in THF for 1 hr after the ammonia was evaporated, followed by nitration at −33° and acidification with glacial acetic acid at −50°. Neopentyl 1-dodecanesulfonate (8.01 g, 0.025 mol) gave 4.3 g (47.0%) of **neopentyl 1-nitro-1-dodecanesulfonate**: $n^{20}D$ 1.4560; ir (neat) 1370 and 1178 (SO_2), and 1568 and 1358 cm^{-1} (NO_2); nmr (CCl_4) δ 0.89–1.05 (t, 3, CH_3), 1.0 [s, 9, $C(CH_3)_3$], 1.27 [s, 18, $CH_3(CH_2)_9$], 2.1–2.5 (m, 2, CH_2CH), 3.98 (s, 2, OCH_2), and 5.35–5.60 (q, 1, CH).

Anal. Calcd for $C_{17}H_{35}NO_5S$: C, 55.86; H, 9.65; N, 3.83; S, 8.77. Found: C, 55.92; H, 9.49; N, 3.88; S, 8.50.

Dineopentyl 1,4-dinitro-1,4-butanedisulfonate (68.9%): mp 92° dec ($CHCl_3$); ir (KBr) 1382 and 1181 (SO_2), and 1575 and 1369 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.01 [s, 18 $C(CH_3)_3$], 2.45–2.70 (m, 4, CH_2), 4.08 (s, 4, OCH_2), and 5.45–5.71 (m, 2, CH).

Anal. Calcd for $C_{14}H_{28}N_2O_{10}S_2$: C, 37.49; H, 6.29; N, 6.25; S, 14.30. Found: C, 37.27; H, 6.44; N, 6.35; S, 14.34.

Neopentyl 2-Nitro-2-butanesulfonate (5)—The general procedure was followed except that neopentyl 2-butanesulfonate (10.42 g, 0.05 mol) was used. Filtering off potassium chloride, concentrating the ethereal filtrate *in vacuo*, and eluting the oily residue with benzene on an aluminum oxide (alumina, acid washed) column gave 4.4 g (34.7%) of **5**: mp 37.5–38.5°; ir (melt) 1360 1183 (SO_2), and 1568 and 1330 cm^{-1} (NO_2); nmr (CCl_4) δ 0.90–1.16 (t, 3, CH_3CH_2), 0.99 [s, 9, $C(CH_3)_3$], 1.95 [s, 3, $C(NO_2)CH_3$], 2.0–2.8 (m, 2, CH_3CH_2), and 3.94 (s, 2, OCH_2).

Anal. Calcd for $C_9H_{19}NO_5S$: C, 42.67; H, 7.56; N, 5.53; S, 12.66. Found: C, 42.95; H, 7.83; N, 5.61; S, 12.64.

Octyl 1-Nitro-1-butanesulfonate (2c), Potassium 1-Nitrobutanesulfonate (3), and 1-Octene (12).—The general procedure was followed except that octyl 1-butylsulfonate (1c) (12.52 g, 0.05 mol) and 250 ml of ammonia were used, and that the nitration time was 5 min at −33°.

After acidification with ammonium chloride (5.89 g, 0.11 mol) and replacement of ammonia with absolute ether, precipitate A was filtered off. The ethereal filtrate (B) was extracted with 10% aqueous potassium hydroxide and the basic extract reacidified with glacial acetic acid and extracted with ether. Drying the combined extracts (Na_2SO_4) and concentrating *in vacuo* gave 3.5 g (23.8%) of **octyl 1-nitro-1-butanesulfonate (2c)**: $n^{20}D$ 1.4451; ir (neat) 1378 and 1180 (SO_2), and 1572 and 1358 cm^{-1} (NO_2); nmr (CCl_4) δ 0.85–1.19 [m, 6, CH_3 and $(CH_2)_6CH_3$], 1.40–2.0 [m, 14, CH_3CH_2 and $(CH_2)_6CH_3$], 2.2–2.75 (m, 2, CH_2CH), 4.32–4.53 (t, 2, OCH_2), and 5.42–5.67 (q, 1, CH).

Anal. Calcd for $C_{12}H_{25}NO_5S$: C, 48.79; H, 8.53; N, 4.74; S, 10.86. Found: C, 48.67; H, 8.59; N, 4.72; S, 10.79.

Concentration of filtrate B *in vacuo* and glpc analysis of the residue showed it to contain **1-octene** (0.22 g, 4.0%), $n^{20}D$ 1.4080 (lit.[10] $n^{20}D$ 1.4087), and 1c (8.2 g, 65.6% recovery).

Continuous extraction of precipitate A with acetone and concentration of the extract *in vacuo* gave **potassium 1-nitrobutanesulfonate (3)** (0.9 g, 8.1%): mp 234° dec (95% ethanol); ir (KBr) 1210 and 1052 (SO_2), and 1552 and 1360 cm^{-1} (NO_2); nmr ($DMSOd_6$) δ 0.78–1.01 (t, 3, CH_3), 1.08–1.65 (m, 2, CH_3CH_2), 1.92–2.4 (m, 2, CH_2CH), and 5.26–5.51 (q, 1, CH).

Anal. Calcd for $C_4H_8KNO_5S$: C, 21.71; H, 3.64; K, 17.67; N, 6.33; S, 14.49. Found: C, 21.71; H, 3.86; K, 17.45; N, 6.26; S, 14.37.

Ethyl 1-Nitro-1-butanesulfonate (2a) and Compound 3.—By following the procedure for preparing compound 2c, there were obtained 10.8% potassium salt **3** and 54.8% **ethyl 1-nitro-1-butanesulfonate**: bp 80–82° (0.025 mm); $n^{20}D$ 1.4450; ir (neat)

(5) T. B. Johnson and J. M. Sprague, *J. Amer. Chem. Soc.*, **58**, 1348 (1936).

(6) J. M. Sprague and T. B. Johnson, *ibid.*, **59**, 1837 (1937).

(7) W. E. Truce and L. W. Christensen, *J. Org. Chem.*, **33**, 2261 (1968).

(8) *Caution!* The first drops of alkyl nitrate should be added slowly because a considerable exotherm develops.

(9) Attempted vacuum distillation at < 0.001 mm resulted in decomposition.

(10) A. F. Forziati, D. L. Camin, and F. D. Rossini, *J. Res. Nat. Bur. Stand. A*, **45**, 406 (1950).

1380 and 1180 (SO_2), and 1572 and 1365 cm^{-1} (NO_2); nmr (CCl_4) δ 0.91–1.13 (t, 3, CH_3CH_2), 1.32–1.58 (t, 3, OCH_2CH_3), 1.58–2.0 (m, 2, CH_3CH_2), 2.18–2.70 (m, 2, CH_2CH), 4.28–4.65 (q, 2, OCH_2), and 5.48–5.72 (q, 1, CH).

Anal. Calcd for $C_6H_{13}NO_5S$: C, 34.12; H, 6.20; N, 6.63; S, 15.18. Found: C, 34.39; H, 6.27; N, 6.56; S, 15.40.

Ethyl 3-Methyl-3-pentanesulfonate (8) and Potassium 2-Nitro-2-butanesulfonate (7).—The procedure was similar to the preparation of **2b** except that ethyl 2-butanesulfonate (8.31 g, 0.05 mol) was used. Filtering off the potassium chloride precipitate and concentrating the filtrate *in vacuo* gave 3.4 g (35.1%) of compound **8** as determined by glpc analysis: $n^{20}D$ 1.4438; ir (neat) 1344 and 1183 cm^{-1} (SO_2); nmr (CCl_4) δ 0.86–1.09 [t, 6, $(CH_3CH_2)_2C$], 1.25–1.49 (t, 3, OCH_2CH_3), 1.28 [s, 3, $C(CH_3)$], 1.61–2.0 [m, 4, $(CH_3CH_2)_2C$ and 4.0–4.35 (q, 2, OCH_2).

Anal. Calcd for $C_8H_{18}O_3S$: C, 9.45; H, 9.34; S, 16.51. Found: C, 49.73; H, 9.53; S, 16.68.

Extracting the precipitate continuously with acetone, concentrating the extract *in vacuo*, and recrystallizing the residue three times with 95% ethanol gave 5.9 g (53.1%) of **7**: mp 244° dec; ir (KBr) 1205, and 1038 (SO_2), and 1538 and 1338 cm^{-1} (NO_2); nmr (D_2O) δ 0.88–1.13 (t, 3, CH_3CH_2), 1.96 [s, 3, $C(NO_2)CH_3$], and 2.0–3.0 (m, 2, CH_3CH_2).

Anal. Calcd for $C_4H_8KNO_5S$: C, 21.71; H, 3.64; K, 17.67; N, 6.33; S, 14.49. Found: C, 21.51; H, 3.82; K, 17.90; N, 6.51; S, 14.76.

Treatment of Ethyl 1-Butanesulfonate (1a) with Potassium Amide at Alkyl Nitrate Nitration Conditions.—To 11.03 g (0.2 mol) of potassium amide in 250 ml of anhydrous ammonia was added at −33° compound **1a** (16.62 g, 0.10 mol). After the reaction mixture stirred for 5 min, ammonium chloride (11.24 g, 0.21 mol) was added at −50° and the ammonia replaced by anhydrous ether. Filtering off potassium chloride, concentrating the filtrate *in vacuo*, and distilling the residue gave 15.3 g (92.2% recovery) of **1a**: bp 70–73° (0.7 mm); $n^{20}D$ 1.4348.

Treatment of Ethyl 2-Butanesulfonate (6) with Potassium Amide at Alkyl Nitrate Nitration Conditions.—The procedure was similar to the treatment of compound **1a** with potassium amide. Ethyl 2-butanesulfonate (**6**) (8.31 g, 0.05 mol) was recovered in 93.4% yield: bp 65° (0.2 mm); $n^{20}D$ 1.4310.

Conversion of Ethyl 1-Nitro-1-butanesulfonate (2a) to Potassium 1-Nitro-1-butanesulfonate (3).—The procedure was similar to the treatment of **1a** with potassium amide except that ethyl 1-nitro-1-butanesulfonate (**2a**) (10.56 g, 0.05 mol) was used. After replacing the ammonia with anhydrous ether, the precipitate was filtered. Extracting the precipitate with acetone and concentrating the extract *in vacuo* gave 2.91 g (26.3%) of **3**: mp 234° dec.

Concentrating the ethereal filtrate *in vacuo* and distilling the residue gave 7.1 g (67.3% recovery) of **2a**: bp 80–82° (0.25 mm); $n^{20}D$ 1.4450.

Conversion of Potassium 1-Ethoxysulfonyl-1-butanenitronate to Ethyl 1-Nitro-1-butanesulfonate (2a).—The procedure was similar to the treatment of **1a** with potassium amide. Potassium 1-ethoxysulfonyl-1-butanenitronate (4.4 g, 0.0177 mol) gave 3.6 g (96.2%) of **2a**: bp 80–82° (0.25 mm); $n^{20}D$ 1.4447.

Deuteration of Neopentyl 1-Dodecanesulfonate.—To 0.36 g (0.0066 mol) of potassium amide in 100 ml of liquid ammonia was added at −33° neopentyl 1-dodecanesulfonate (1.06 g, 0.0033 mol). After 5 min the ammonia was replaced with anhydrous ether and the last traces of ammonia were removed by refluxing for 30 min. The reaction mixture was then cooled to −50° and deuterium oxide (0.30 g, 0.0149 mol) was added. Warming the reaction mixture to room temperature, decanting the clear ethereal layer, and concentrating *in vacuo* gave a mixture of neopentyl 1-dodecanesulfonate and neopentyl 1-dodecanesulfonate-d_1: nmr (CCl_4) δ 2.85–3.15 [t, 1.25, $CH_3(CH_2)_{10}CHD$] (75% of deuterium was incorporated).

Neopentyl 3-Methyl-3-pentanesulfonate (11).—To a solution of potassium amide (3.44 g, 0.0624 mol) in 250 ml of ammonia was added at −33° neopentyl 2-butanesulfonate (**10**) (6.50 g, 0.0312 mol). After stirring the reaction mixture for 5 min, ethyl 3-methyl-3-pentanesulfonate (**8**) (6.04 g, 0.0312 mol) was added in 5 min at −35°. Then acidifying the reaction mixture with ammonium chloride (3.67 g, 0.0686 mol) at −50°, replacing the ammonia with anhydrous ether, filtering the potassium chloride, concentrating the filtrate *in vacuo*, and distilling the residue gave a mixture of compounds **10** and **11**: bp 64° (0.15 mm). Analysis by glpc gave 4.74 g (72.9% recovery) of **10** and 1.55 g (21.1%) of **11**: $n^{20}D$ 1.4450; ir (neat) 1344 and 1184 cm^{-1} (SO_2); nmr (CCl_4) δ 0.86–1.10 [t, 6, $(CH_3CH_2)_2C$], 0.97 [s, 9, $C(CH_3)_3$], 1.28 [s, 3, $C(CH_3)$], 1.62–2.01 [m, 4, $(CH_3CH_2)_2C$], and 3.75 (s, 2, OCH_2).

Anal. Calcd for $C_{11}H_{24}O_3S$: C, 55.89; H, 10.23; S, 13.57). Found: C, 55.79; H, 10.36; S, 13.35.

Neopentyl 1-Bromo-1-nitroethanesulfonate.—The following experiment is typical of the method used for the bromination of α-nitroalkylsulfonates. To a solution of 0.66 g (0.01 mol) 85% potassium hydroxide in 50 ml of absolute ethanol was added with stirring at 0–5° neopentyl 1-nitro-1-ethanesulfonate (2.37 g, 0.106 mol). Allowing the reaction mixture to warm to room temperature, concentrating the clear solution *in vacuo*, slurrying the solid residue in ether, and filtering gave 2.63 g (100%) of crude potassium 1-neopentoxysulfonyl-1-ethanenitronate.

To a slurry of the crude salt (2.63 g, 0.01 mol) in 50 ml of carbon tetrachloride was added in 15 min at 0–5° bromine (1.60 g, 0.01 mol), and then stirring was continued for 1 hr at room temperature. Filtering off potassium bromide, concentrating the filtrate *in vacuo*, dissolving the residue in ether, and washing the ethereal solution successively with 0.5% sodium bisulfite, 1% potassium hydroxide, and water, followed by drying (sodium sulfate), and concentrating *in vacuo* gave 2.87 g (94.2%) of analytically pure **neopentyl 1-bromo-1-nitroethanesulfonate**: mp 33–35°; ir (melt) 1372 and 1186 (SO_2), and 1570 and 1375 cm^{-1} (NO_2); nmr (CCl_4) δ 1.05 [s, 9, $C(CH_3)_3$], 2.62 (s, 3, CH_3), and 4.20 (s, 2, OCH_2).

Anal. Calcd for $C_7H_{14}BrNO_5S$: C, 27.64; H, 4.64; Br, 26.27; N, 4.61; S, 10.54. Found: C, 27.62; H, 4.74; Br, 26.42; N, 4.67; S, 10.51.

Neopentyl 1-bromo-1-nitrobutanesulfonate (85%) was analyzed as follows: $n^{20}D$ 1.4759; ir (neat) 1385 and 1183 (SO_2), and 1575 and 1368 cm^{-1} (NO_2); nmr (CCl_4) δ 0.95–1.15 (t, 3, CH_3), 1.03 [s, 9, $C(CH_3)_3$], 1.36–1.88 (m, 2, CH_3CH_2), 2.5–2.9 (m, 2, CH_2C), and 4.12 (s, 2, OCH_2).

Anal. Calcd for $C_9H_{18}BrNO_5S$: C, 32.54; H, 5.46; Br, 24.05; N, 4.22; S, 9.65. Found: C, 32.68; H, 5.38; Br, 24.07; N, 4.18; S, 9.78.

Ethyl 1-bromo-1-nitrobutanesulfonate (47.1%) was analyzed as follows: bp 78–80° (0.3 mm); $n^{20}D$ 1.4822; ir (neat) 1390 and 1182 (SO_2), and 1575 and 1380 cm^{-1} (NO_2); nmr (CCl_4) δ 0.98–1.18 (t, 3, CH_3), 1.4–1.65 (t, 3, OCH_2CH_3), 1.70–2.1 (m, 2, CH_3CH_2), 2.3–3.1 (m, 2, CH_2C), and 4.5–4.83 (q, 2, OCH_2).

Anal. Calcd for $C_6H_{12}BrNO_5S$: C, 24.84; H, 4.17; Br, 27.54; N, 4.83; S, 11.05. Found: C, 24.78; H, 4.18; Br, 27.25; N, 5.02; S, 10.99.

Dineopentyl 1,4-dibromo-1,4-dinitro-1,4-butanedisulfonate (74.0%) was analyzed as follows: mp 77° dec (CCl_4); ir (KBr) 1388 and 1180 (SO_2), and 1575 and 1370 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.02 [s, 18, $C(CH_3)_3$], 3.10 (s, 4, CH_2), and 4.18 (s, 4, OCH_2).

Anal. Calcd for $C_{14}H_{26}Br_2N_2O_{10}S_2$: C, 27.73; H, 4.32; Br, 26.36; N, 4.26; S, 10.58. Found: C, 27.50; H, 4.50; Br, 26.20; N, 4.47; S, 10.57.

Neopentyl 1-bromo-1-nitrohexanesulfonate (76.8%) was analyzed as follows: $n^{20}D$ 1.4710; ir (neat) 1388 and 1184 (SO_2), and 1582 and 1374 cm^{-1} (NO_2); nmr (CCl_4) δ 0.92–1.02 (t, 3, CH_3), 1.02 [s, 9, $C(CH_3)_3$], 1.2–1.5 [s, 6, $CH_3(CH_2)_3$], 2.5–3.0 (m, 2, CH_2C), and 4.12 (s, 2, OCH_2).

Anal. Calcd for $C_{11}H_{22}BrNO_5S$: C, 36.67; H, 6.16; Br, 22.18; N, 3.89; S, 8.90. Found: C, 36.75; H, 5.94; Br, 22.23; N, 3.87; S, 8.86.

Registry No.—**1b**, 25056-20-6; **1c**, 25056-18-2; **2b**, 25056-19-3; **2c**, 25056-21-7; **3**, 25056-22-8; **4**, 25056-23-9; **5**, 25056-41-1; **6**, 25056-24-0; **7**, 25056-25-1; **8**, 25056-26-2; **10**, 25056-27-3; **11**, 25056-28-4; neopentyl ethenesulfonate, 25056-29-5; neopentyl 1-hexanesulfonate, 25056-30-8; neopentyl 1-octanesulfonate, 25056-31-9; neopentyl 1-decanesulfonate, 25056-32-0; neopentyl 1-dodecanesulfonate, 25056-33-1; dineopentyl 1,4-butanedisulfonate, 25056-34-2; neopentyl 1-nitro-1-ethanesulfonate, 25056-35-3; neopentyl 1-nitro-1-hexanesulfonate, 25056-36-4; neopentyl 1-nitro-1-octanesulfonate, 25056-37-5; neopentyl 1-nitro-1-decanesulfonate, 25056-38-6; neopentyl 1-nitro-1-dodecanesulfonate, 25056-39-7; dineopentyl 1,4-dinitro-

1,4-butanedisulfonate, 25056-40-0; ethyl 1-nitro-1-butanesulfonate, 25056-42-2; neopentyl 1-bromo-1-nitroethanesulfonate, 25056-43-3; neopentyl 1-bromo-1-nitrobutanesulfonate, 25056-44-4; ethyl 1-bromo-1-nitrobutanesulfonate, 25056-45-5; dineopentyl 1,4-dibromo-1,4-dinitro-1,4-butanedisulfonate, 25056-46-6; neopentyl 1-bromo-1-nitrohexanesulfonate, 25056-47-7.

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Formation, Proof of Structure, and Thermal Decomposition of Peroxide from Benzyl Mesityl Ketone[1]

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Experimental conditions for autoxidation of benzyl mesityl ketone to a peroxide were investigated. The peroxide was characterized as 2-hydroperoxy-2-phenyl-2′,4′,6′-trimethylacetophenone (III) by ir and ^{1}H nmr spectra, and iodide reduction to the known 2,4,6-trimethylbenzoin (IV). Solid-state thermal decomposition of III forms mesitoic acid and benzaldehyde in equal amounts by one pathway and mesityl phenyl diketone (V) and water by another. The latter is a new mode of thermal decomposition for α-keto hydroperoxides. Decomposition also takes place slowly by both pathways at room temperature on standing in contact with a glass surface. Differential thermal analysis and differential scanning calorimetry studies under various conditions show that decomposition of III occurs in the solid phase without prior melting. A mechanism is proposed for the two modes of decomposition.

In a previous paper[4] on the autoxidative cleavage of isopropyl mesityl ketone to mesitoic acid and acetone,[5] an intermediate peroxide was detected but could not be isolated for characterization. A study of time sequential infrared spectra of oxidation mixtures indicated the α-keto hydroperoxide structure (Ia) in preference to an isomeric oxaoxetane formulation (Ib) (Scheme I). Kohler who was the first to report[6] a stable keto peroxide formulated structures analogous to Ib.[7] Rigaudy observed[8] ultraviolet absorption in the carbonyl region for Kohler's keto peroxides and formulated their structures as keto hydroperoxides analogous to Ia; carbonyl bands in the infrared spectra were reported by Fuson and Jackson[9] in confirmation of Rigaudy's formulation. The present paper reports the formation, characterization by infrared and ^{1}H nmr spectra and chemical methods, and thermal decomposition of a stable peroxide isolated from autoxidation of benzyl mesityl ketone (II)[10] which was originally prepared for use in studies of structures of Grignard compounds derived from hindered ketones.[13]

Results and Discussion

Autoxidation.—The samples of benzyl mesityl ketone (II) were obtained as liquids[14] which solidified or precipitated peroxides after standing in stoppered or unstoppered vessels for varying lengths of time (15 days to 6 months). A number of qualitative observations were made on autoxidative behavior of II in order to ascertain conditions under which oxidation could be accelerated or minimized. The random nature of the autoxidations was evident from 15 experiments[15] which were carried out. The following observations can be made. Autoxidation proceeded as readily (1) when apparatus was flushed with nitrogen as when allowed to stand in contact with air, (2) when oxygen was bubbled through the liquid or a solution or allowed to stand, and (3) whether exposed to light or shielded from it. Traces of oxygen appeared to be sufficient to result in autoxidation. In one experiment no peroxide precipitate was observed[16] when the sample was allowed to stand undisturbed exposed to air for 11 months. The recommended procedure for conducting the autoxidation is simply to allow the liquid ketone to stand in a vessel with maximum surface area exposed to the atmosphere and to agitate the sample occasionally. The best conditions found for minimizing autoxidation of II were to carry out preparation and handling of the compound in a rigorously deoxygenated nitrogen atmosphere and to store the compound at low temperature.

Spectral and Chemical Proof of Structure of Peroxide III.—Ir and ^{1}H nmr spectra are consistent with an α-keto hydroperoxide structure (III). The ir spectrum

(1) A. G. Pinkus, M. Z. Haq, and J. G. Lindberg, Abstracts, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, ORGN-59.

(2) Robert A. Welch Foundation postdoctoral fellow.

(3) Robert A. Welch Foundation predoctoral fellow.

(4) A. G. Pinkus, W. C. Servoss, and K. K. Lum, *J. Org. Chem.*, **32**, 2619 (1967).

(5) Water was also found to be a product.

(6) E. P. Kohler, *Amer. Chem. J.* **36**, 177, 529 (1906).

(7) E. P. Kohler and R. B. Thompson, *J. Amer. Chem. Soc.*, **59**, 887 (1937).

(8) J. Rigaudy, *C. R. Acad. Sci., Paris*, **226**, 1993 (1948).

(9) R. C. Fuson and H. L. Jackson, *J. Amer. Chem. Soc.*, **72**, 1637 (1950).

(10) Two recent papers on α-keto hydroperoxides have appeared. One paper[11] mainly concerned with hydrogen-bonding aspects of two keto hydroperoxides was published when the present work was well under way. When this paper appeared we discontinued our ir and ^{1}H nmr studies on hydrogen bonding of the hydroperoxides but completed other aspects of the problem. A second paper[12] which appeared after the present work was complete, deals with preparation and properties of aliphatic α-keto hydroperoxides.

(11) W. H. Richardson and R. F. Steed, *J. Org. Chem.*, **32**, 771 (1967).

(12) F. C. P. Cubbon and C. Hewlett, *J. Chem. Soc. C*, 2978 (1968).

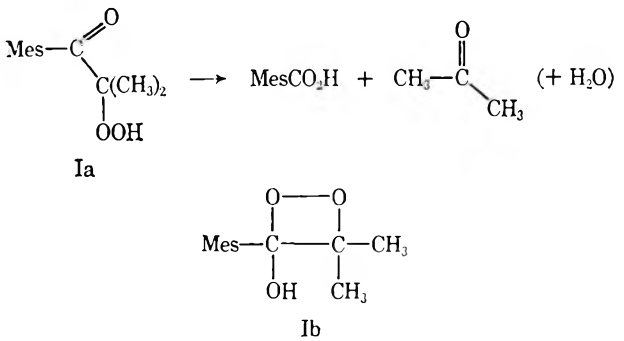
(13) A. G. Pinkus, J. G. Lindberg, and A. B. Wu, *ibid.*, *D*, 1351 (1969).

(14) E. H. Weinstock, Jr., and R. C. Fuson, *J. Amer. Chem. Soc.*, **58**, 1233 (1936), report mp 32.0–32.5°.

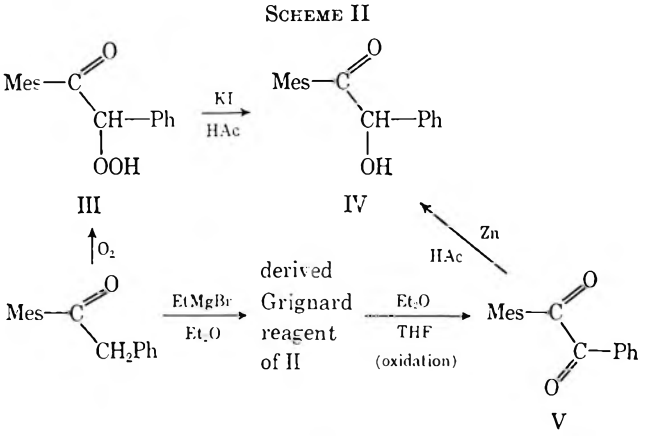
(15) A table summarizing the results of these experiments was eliminated from the original paper to save space.

(16) An ir spectrum of the mother liquor from one of the experiments showed no detectable amount of peroxide; this would indicate solubility of peroxide to be low in this mixture. Although peroxide was not tested for in this sample, it is possible that it could have been present in solution in small amount.

SCHEME I



SCHEME II



of III showed a carbonyl stretching band, an –O–O– band, and O–H stretching bands (for –OOH). Similar carbonyl and –OO–H stretching bands were observed in the present investigation for 3,3-diphenyl-2-hydroperoxy-2′,4′,6′-trimethylpropiophenone[17] (one of "Kohler's peroxides").

The ^{1}H nmr spectrum[19] of III showed a singlet at 9.62 ppm for the OOH proton. (Other chemical shifts are in the Experimental Section.) Hydroperoxy protons show characteristic low-field absorption[20] indicating considerable deshielding. For the only previously reported ^{1}H nmr absorption for an α-keto hydroperoxide, Richardson and Steed[11] listed 9.39 ppm for the hydroperoxy proton of 2,4-dimethyl-2-hydroperoxy-3-pentanone. The corresponding signal for 3,3-diphenyl-2-hydroperoxy-2′,4′,6′-trimethylpropiophenone observed in the present work was at 9.28 ppm.

III gave a positive iodide test for active oxygen. A quantitative determination using an iodometric titration method[21] showed one active oxygen per molecule of III. For a chemical proof of structure, hydroperoxide III on reduction with potassium iodide was converted into 2,4,6-trimethylbenzoin (IV); the latter was previously prepared by Fuson and coworkers by zinc–acetic acid reduction of mesityl phenyl diketone (V)[14] (Scheme II) and aluminum chloride catalyzed condensation of mesitylglyoxal and benzene.[22]

Thermal Decomposition of 2-Hydroperoxy-2-phenyl-2′,4′,6′-trimethylacetophenone (III).—On heating in a flame, III decomposed explosively. Under milder conditions[23] the following products of decomposition were isolated and characterized: mesitoic acid, benzaldehyde, mesityl phenyl diketone (V),[24] and water. Quantitative determinations of the amounts of products showed that mesitoic acid (49% average yield) and benzaldehyde were formed in equivalent amounts; this fact is important in the consideration of a mechanism for the decomposition. This result contrasts with that reported previously[4] for the autoxidative cleavage of isopropyl mesityl ketone where the molar quantity of acetone exceeded that of mesitoic acid (ratio of 0.709:0.478 = 1.48).[25] Because of experimental difficulties it was not possible to determine the amount of water quantitatively in the present investigation.

α-Keto hydroperoxides are reported[26] to decompose thermally to carboxylic acids and aldehydes or ketones. The present investigation shows that an additional mode of thermal decomposition to an α,β diketone and water can occur simultaneously. The two different pathways are summarized in Scheme III. The total overall yield for the two pathways (average of three experiments) was 60%.[27]

Decomposition was also studied by differential thermal analysis (DTA) and differential scanning calorimetry (DSC). It was of particular interest to ascertain by these techniques whether or not the hydroperoxide melted and then decomposed, or whether direct decomposition of the solid took place. In previous reports[6,7,9,28] keto hydroperoxides have been stated to decompose at or slightly above their melting points. The two alternatives should be readily distinguishable by DTA or DSC since prior melting followed by decomposition would be expected to produce two peaks, one endothermic owing to melting followed closely by an exothermic decomposition peak, whereas only a single peak (probably exothermic)[29] would be expected for direct decomposition of solid hydroperoxide. Only a single[30] sharp exothermic peak was observed using both

(17) Originally prepared by Kohler, *et al.*;[6,7,18] ir and ^{1}H nmr spectra first obtained and reported in the present work.

(18) E. P. Kohler and C. E. Barnes, *J. Amer. Chem. Soc.*, **55**, 690 (1933); E. P. Kohler, M. Tishler, and H. Potter, *ibid.*, **57**, 2517 (1935).

(19) ^{1}H nmr spectra for III and the "Kohler peroxide" are the first to be reported for aromatic keto hydroperoxides; the only previous complete ^{1}H nmr spectrum given for a keto hydroperoxide was for an aliphatic derivative.[11]

(20) S. Fujiwara, M. Katayama, and S. Kamio, *Bull. Chem. Soc. Jap.*, **32**, 657 (1959); D. Swern, A. H. Clements, and T. M. Luong, *Anal. Chem.*, **41**, 412 (1969).

(21) M. V. Goftman and G. D. Kharlampovich, *J. Appl. Chem. USSR*, **30**, 465 (1957) [*Zh. Prikl. Khim.*, **30**, 439 (1957)].

(22) R. C. Fuson, H. H. Weinstock, Jr., and G. E. Ullyot, *J. Amer. Chem. Soc.*, **57**, 1803 (1935).

(23) Controlled heating in air, *in vacuo* under nitrogen, or at atmospheric pressure; the same products were found under these varied conditions. Decomposition on a vpc column at 200° was also studied; the peak for benzaldehyde was identified conclusively.

(24) Mesityl phenyl diketone (V) was also obtained in the present work in 7.9% yield during an attempted preparation of the enol ether of benzyl mesityl ketone (II) by methylation of the derived bromo Grignard reagent of II, oxidation having taken place.

(25) A tentative explanation for deviation from the expected 1:1 ratio has been presented.[4]

(26) Earlier work is reviewed by E. G. E. Hawkins, "Organic Peroxides," Van Nostrand, Princeton, N. J., 1961, pp 116, 381 ff; L. Horner, "Autoxidation and Antioxidants," Vol. I, W. O. Lundberg, Ed., Interscience, New York, N. Y., 1961, Chapter 5; A. G. Davies, "Organic Peroxides," Butterworths, London, 1961.

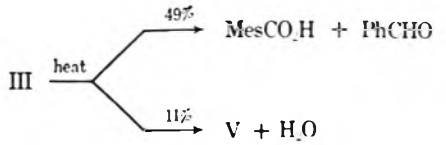
(27) An unidentified residue accounted for the remaining 40% from decomposition of III after separation and analysis of products as described. Several preliminary experiments were carried out to establish optimum conditions for decomposition.

(28) R. C. Fuson, E. W. Maynert, and W. J. Shenk, Jr., *J. Amer. Chem. Soc.*, **67**, 1939 (1945).

(29) This would depend on the relative magnitude of the enthalpy of decomposition compared with that of fusion.

(30) Other peaks appeared at much higher temperatures owing to vaporization and possible further decomposition of products of initial decomposition. During observations taken while obtaining the melting point of III, the material in the capillary after decomposition was liquid. Furthermore, DTA and DSC curves did not show any peaks corresponding to melting points of mesitoic acid and mesityl phenyl diketone, indicating that these were in a molten state.

SCHEME III

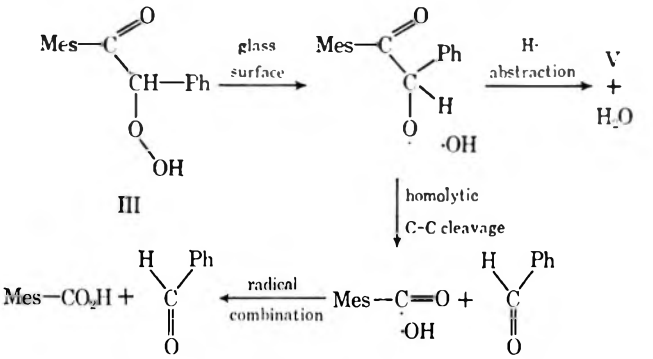


DSC and DTA under all conditions studied showing that the solid decomposed directly without first melting. Temperatures of decomposition (average) were 135° with DTA and 139.8° with DSC.

Stability of Hydroperoxide (III).—Freshly prepared samples of III having a white crystalline appearance slowly turned yellow[31] after standing at room temperature in stoppered glass containers whether kept in the dark or exposed to ordinary daylight. The odor of benzaldehyde was also evident. These observations show that both modes observed for thermal decomposition are also operative for slow room temperature decomposition. An interesting aspect of the decomposition was that only material in contact with the glass container turned yellow in samples examined; material in the interior of the sample or on top was unchanged.[32] Evidently decomposition is catalyzed by contact with the glass surface.[33] Freshly prepared samples of peroxide III showed no detectable[36] decomposition after standing in stoppered vials for nearly two years in a refrigerator.

Mechanism of Thermal Decomposition.—Mechanisms of thermal decompositions of alkyl hydroperoxides have been extensively investigated[26,35,37] although much less work has been done on α-keto hydroperoxides. The following proposed tentative mechanism[38] (Scheme IV) for solid-state thermal decomposition of III is adapted from mechanisms for other hydroperoxide decompositions.[35,37] The initiation step is postulated as cleavage of the O–O bond. Although Benson[39] showed that homolysis of the peroxide bond contributed negligibly to kinetics of decomposition of *t*-butyl hydroperoxide *in solution*, adsorption on the glass wall surface in the case of the *solid* keto hydroperoxide at the peroxy oxygens could result in a lowering of the energy of activation in the latter case. The second step could take place in two ways. Abstraction of the α-hydrogen atom by hydroxyl radical would form mesityl phenyl diketone and water. In the other pathway, homolytic cleavage of the carbon–carbon bond would

SCHEME IV



give benzaldehyde and mesitoyl radical; in a radical combination step the latter would react with hydroxyl radical to form mesitoic acid. These pathways account for *ca.* 60% of the products. The remaining 40% of products could be formed by other reactions of the two radicals formed in the first step. Since mesitoic acid and benzaldehyde are formed in nearly equal amounts, it is unlikely that the mesitoyl radical undergoes any reaction other than combination with hydroxyl to form mesitoic acid. Thus, the remaining products must be formed at some other stage of the reaction or by some other pathway. Although 2,4,6-trimethylbenzoin (IV) would be expected to be formed by abstraction of a proton by the initial cleavage fragment (other than hydroxyl), the ir spectrum of the residue showed a carbonyl band only at 1818 cm^{-1}, whereas IV has this band at 1685 cm^{-1}; this shows the absence of IV.

Experimental Section[40]

Benzyl Mesityl Ketone (II).—II was prepared in 68–79% yield by Friedel–Crafts reaction[41] of mesitylene and phenylacetyl chloride in petroleum ether (bp 65–110°) using aluminum chloride and also by polyphosphoric acid[42] catalyzed condensation[43] of mesitylene and phenylacetic acid in 56.5% yield. The product was distilled under nitrogen: bp 160–165° (<1 mm); ir[44] (neat) 1682 cm^{-1} (C=O); ^1H nmr[45] (CCl_4) 7.14 (5, C_6H_5), 6.69 (2, Mes-H_2), 3.82 (2, CH_2), 2.18 (3, *p*-CH_3), 1.99 (6, *o*-CH_3).

Autoxidation of Benzyl Mesityl Ketone (II) to 2-Hydroperoxy-2-phenyl-2′,4′,6′-trimethylacetophenone (III).—II on standing in various containers at room temperature autoxidized to III. The time period for autoxidation of II and the yields of III varied from 7 to 8% (for those determined) depending on conditions;

(31) The change was noticeable after 3–4 months; in a separate experiment the yellow substance was identified as mesityl phenyl diketone (V) by means of thin layer chromatography.

(32) This observation suggests the possibility that decomposition at room temperature might be prevented or slowed in other types of containers made of plastic, *etc.*; however, this was not investigated. Conversely, in the cases studied, thermal decomposition is evidently initiated on the glass or metal surface (spatula, DSC and DTA surfaces).

(33) A difference in rates of decomposition of *t*-butyl hydroperoxide in solution was noted by Bulygin and Zaikov[34] for glass and metallic reactors. They attributed the change in rate to the nature of the reactor wall. Hiatt and Irwin[35] reported that the first-order rate constant for decomposition of a solution of *t*-butyl hydroperoxide was increased by 60% when the surface to volume ratio was increased sevenfold by using crushed Pyrex tubing.

(34) M. G. Bulygin and G. E. Zaikov, *Bull. Acad. Sci. USSR*, 481 (1968) [*Izv. Akad. Nauk SSSR*, 491 (1968)].

(35) R. Hiatt and K. C. Irwin, *J. Org. Chem.*, **33**, 1436 (1968).

(36) No benzaldehyde odor, yellow color formation, or melting point change.

(37) The recent series of papers by R. Hiatt and coworkers summarize the current state of knowledge in this area: R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.*, **33**, 1416 (1968); R. Hiatt, T. Mill, K. C. Irwin, and J. K. Castleman, *ibid.*, 1421, 1428, (1968); R. Hiatt, K. C. Irwin, and C. W. Gould, *ibid.*, 1430 (1968); ref 35. The paper by Bulygin and Zaikov[34] is a leading reference to recent Russian work in this area.

(38) The editor suggested another possible mechanism for formation of acid and aldehyde by intramolecular reaction of the oxygen of the peroxygen linkage with the carbonyl carbon of III which would afford a species which could decompose directly to acid and aldehyde. Another possible mechanism previously considered was addition of the hydroperoxy proton and oxygen across the carbonyl to form an intermediate analogous to Ih which could then undergo fragmentation to form acid and aldehyde by one pathway and diketone and water by another.

(39) S. W. Benson, *J. Chem. Phys.*, **40**, 1007 (1964).

(40) Melting points are corrected; boiling points are uncorrected.

(41) A. Klages and G. Lickroth, *Chem. Ber.*, **32**, 1549 (1899).

(42) The authors thank FMC Corp. for a sample of 115% polyphosphoric acid.

(43) Conditions for the preparation were determined from reactions described in reviews on polyphosphoric acid condensations: F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958); F. Uhlig and H. R. Snyder in "Advances in Organic Chemistry, Methods and Results," R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Vol. I, Interscience, New York, N. Y., 1960, pp 35–81.

(44) Frequencies in cm^{-1}; vs = very strong, s = strong, m = medium, w = weak, sh = shoulder, br = broad, sp = sharp.

(45) δ in parts per million from tetramethylsilane as internal reference; s = singlet, br = broad m = multiplet; relative peak areas in parentheses.

optimum procedure was to allow II to stand with maximum surface area exposed to air with occasional agitation. Two analytical samples were prepared. The first sample[46] was recrystallized from carbon tetrachloride and then from *n*-hexane, mp[47] 125.5–126.2° dec. The second sample[48] after washing with several portions of *n*-hexane melted[47] at 130–132° dec. After two recrystallizations from ethyl acetate, III had mp[47] 134–135° dec. *Anal.* Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.54,[46,49] 75.65[48,50]; H, 6.64,[46,49] 6.78.[48,50] The following spectral data were obtained: ir[44] 1680 (CH_2Cl_2), 1698 (Nujol) (C=O), 888 (Nujol) (-O-O-), 3470[51] (intramolecularly bonded OH), 3330 (CH_2Cl_2) (sh) (intermolecularly bonded OH). Only the 3330 cm^{-1} band appeared for the solid (Nujol mull). ^1H nmr[45] (CCl_3Br and $CDCl_3$ solvents, respectively, for each data set reported): 9.36 (1), 9.62 (OOH); 7.08 (5), 7.28 (C_6H_5); 6.54 (2), 6.74 (Mes-H_2); 5.72 (1), 5.99 [CH(Ph)OO]; 2.19 (3), 2.22 (*p*-CH_3); 1.86 (6), 1.91 (*o*-CH_3).

Preparation of 3,3-Diphenyl-2-hydroperoxy-2′,4′,6′-trimethylpropiophenone.—Benzalacetomesitylene, mp 61°[52] (recrystallized from petroleum ether, bp 30–60°), was prepared in 94% yield by base-catalyzed condensation of acetomesitylene and freshly distilled benzaldehyde by the method of Kohler and Barnes.[18] β,β-Diphenylethyl mesityl ketone, mp[53] 82–83° (from carbon tetrachloride, then absolute ethanol), was prepared by 1,4 addition of phenylmagnesium bromide to benzalacetomesitylene; ir 1685 cm^{-1} (C=O). The peroxide was prepared by oxidation of the enolate of the ketone following the procedure of Kohler and Thompson:[7] 62.5% yield; mp 100–101° (from *n*-hexane);[54] ir[44] 3470[51] (CH_2Cl_2), 3509 (CCl_4),[55] 3410 (sh) (Nujol) (OOH) (intramolecular), 3360 (sh) (CH_2Cl_2), 3390 (Nujol) (OOH) (intermolecular), 1704 (CCl_4)[55] (C=O); ^1H nmr[45] (CCl_3CN solvent except where noted) 9.31 (br,[56] 1), 9.28 (CCl_4)[55] (OOH), 7.17 (br, 10, C_6H_5), 6.70 (s, 2, Mes-H_2), 4.53 ($CHPh_2$),[57] 4.75 [CH(Ph)OO–],[57] 2.33 (s, 3, *p*-CH_3), 1.88 (s, 6, *o*-CH_3).

Reduction of Hydroperoxide III to 2,4,6-Trimethylbenzoin (IV).—A solution of III (0.2025 g, 7.500×10^{-4} mol) in glacial acetic acid (15 ml) was added dropwise over a 15-min period to a stirred solution of potassium iodide (0.500 g, 3.01×10^{-3} mol) in glacial acetic acid (20 ml). The reaction mixture became dark brown owing to liberated iodine. A solution of sodium thiosulfate (*ca.* 0.1 *N*) was added to the reaction mixture until the latter became colorless. The contents were extracted with several 25-ml portions of ether. Combined ether extracts were washed with dilute sodium hydroxide solution and water several times. The ether solution was dried with anhydrous sodium sulfate. On evaporation of ether, 2,4,6-trimethylbenzoin (IV) (0.182 g, 90% yield) was obtained. After recrystallization from ethanol, IV melted at 100–101° (lit.[22] 102°): ir (CH_2Cl_2) 3445 (sp, OH), 1685 cm^{-1} (C=O).

Thermal Decomposition of 2-Hydroperoxy-2-phenyl-2′,4′,6′-trimethylacetophenone (III). Separation and Characteristics of Products.—Crystalline III on heating at 100–110° (oil bath temperature, 1 mm) for 1.5 hr turned yellow. On prolonged heating (6 hr), a sublimate (see below) consisting of mixed yellow and white crystals was obtained; a distillate (colorless droplets) was also collected in a liquid air trap. The inhomogeneous distillate had a bitter almond-like odor characteristic of benzaldehyde. Anhydrous copper sulfate sprinkled on the distillate turned blue instantaneously indicating the presence of water. The ir spectrum (neat) of the distillate (after drying with anhydrous sodium sulfate) showed the same bands as a spectrum of authentic benzaldehyde.

A dilute solution of sodium hydroxide was added to the sublimate of white and yellow crystals from above. The white portion of sublimate dissolved. The yellow insoluble portion was dissolved in ether and the two layers were separated. When the alkaline solution was acidified with dilute hydrochloric acid a white precipitate formed which was collected by filtration and washed with water. After sublimation at 115–120° (oil bath temperature, 1 mm), the crystals had mp 154–155°.[59] The melting point of the mixture of mesitoic acid from the sublimate and an authentic sample was undepressed. The material on thin layer chromatography[60] showed only one spot, R_f 0.32 (*via* uv light) which had the same mobility as that of an authentic sample of mesitoic acid. A comparison of the ir spectrum of the sample with that of authentic material also confirmed the identity of the sublimate as mesitoic acid.

The yellow ether solution from above was washed with water, dried over anhydrous sodium sulfate, and filtered. On removal of ether with a rotary evaporator, yellow crystals were obtained. After recrystallization from petroleum ether (bp 30–60°), the material melted at 136–137°. The compound showed one tlc[60] spot (R_f 0.73); the R_f value corresponded with that from an authentic sample of mesityl phenyl diketone (V). The ir[44] spectrum[61] (Nujol) of V showed absorption bands at 1670 (sh), 1665 (vs, conjugate C=O), 1612 (s, ArC=C), 1600 (s), 855 (vs, mesityl), 730 (s), and 698 (m, monosubstituted phenyl). The ir spectrum of the material showed the same bands as those in a spectrum of an authentic sample of V. A mixture melting point with authentic V was undepressed. ^1H nmr[45,58b] spectral assignments (15% w/v in CCl_4) were 8.15 (AB pattern), 7.6 (A_2B pattern, C_6H_5), 6.83 (2, Mes-H_2), 2.30 (3, *p*-CH_3), 2.22 (6, *o*-CH_3). The compound formed a 2,4-dinitrophenylhydrazone derivative, mp 234–236° (lit.[14] 232.0–232.5°), ir 1668 cm^{-1} (Nujol) (C=O).

Benzaldehyde, mesitoic acid, V, and water were also obtained on heating hydroperoxide III at atmospheric pressure in a flask maintained at 150° (oil bath temperature); decomposition occurred in a few minutes under these conditions. Heating was continued for 6 hr at 100–110° (1 mm) to obtain a distillate (consisting of benzaldehyde and water) and a sublimate (consisting of mesitoic acid and V). A sticky brownish residue whose ir spectrum showed a carbonyl band at 1815 cm^{-1} remained in the flask. The residue appeared to be a complex mixture as evidenced by tlc and was not investigated further.

A solution of peroxide III in CH_2Cl_2 (or $CHCl_3$) was injected into a silicone oil–firebrick vpc column at 200° (240° injector temperature) using helium as carrier gas. Retention time of the benzaldehyde peak was 1.75 min; the peak position was verified by observing the increase in size when a mixture of benzaldehyde and III were injected. No decomposition was observed when the column temperature was at 131° (150° injector temperature).

Quantitative Analysis of Products.—The procedure for a typical run is given. Final procedures were developed after first conducting numerous preliminary experiments in order to optimize yields. Hydroperoxide III (0.175 g, 6.47×10^{-4} mol) covered with glass wool (in order to minimize scattering of III by decomposition) was decomposed in an erlenmeyer flask maintained at 150° (oil bath temperature). The sample turned yellow on decomposition. The flask was removed from the oil bath and the contents were dissolved in sufficient ethanol to make a volume of 25 ml. The amount of mesitoic acid in this mixture was determined by titrating 3-ml portions (diluted with 3 ml each of water and ethanol) with standard aqueous sodium hydroxide using a pH meter.[62] The amount of mesitoic acid in this solution found was 56 mg (53% yield). For two additional experiments with 200 and 222 mg of III, 57 and 62 mg yields were obtained respectively, corresponding to yields of 47 and 46% mesitoic acid. In a separate experiment, it was found that mesitoic acid and benzaldehyde were formed in nearly equivalent

(46) Preparation by J. G. L.

(47) It should be emphasized that these are not melting points but decomposition points as evidenced from DSC and DTA studies.

(48) Preparation by M. Z. H.

(49) Analysis by Galbraith Laboratories, Knoxville, Tenn.

(50) Analysis by M-H-W Laboratories, Garden City, Mich.

(51) Band did not disappear when solution was diluted.

(52) E. P. Kohler, *Amer. Chem. J.*, **38**, 511 (1907), reported mp 63°.

(53) A. N. Nesmeyanov, V. A. Sazonova, and E. B. Landor, *Dokl. Akad. Nauk SSSR*, **63**, 395 (1948) [*Chem. Abstr.*, **45**, 2902 (1951)], reported mp 82°.

(54) Since Kohler and Thompson[8] reported mp 116–117° for their product, the product in the present work (from two separate preparations) was repeatedly recrystallized from the following solvents: *n*-hexane, an ether–petroleum ether mixture, ethanol, methanol, benzene, and a carbon tetrachloride–petroleum ether mixture without a change in the 100–101° mp. The same preparation was also previously carried out[55] in our research group to obtain a product with mp 103.2–103.8° dec (from petroleum ether).

(55) K. K. Lum unpublished work.

(56) Broad peak sharpens to singlet on addition of water.

(57) Assigned tentatively on basis of Dailey and Shoolery's rules.[58a]

(58) R. M. Silverstein and G. C. Bassler "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1963: (a) p 87, (b) pp 59–62.

(59) Melting point of mesitoic acid (Aldrich Chemical Co.) 155°; P. Jannech and M. Weiler, *Chem. Ber.*, **27**, 3446 (1894), reported mp 153–153.4°.

(60) Eastman chromatographic sheet with fluorescent indicator coated with silica gel in benzene:methanol (4:1 ratio).

(61) R. C. Fuson and R. W. Hill, *J. Org. Chem.*, **19**, 1575 (1954).

(62) Control experiments with authentic mesitoic acid were performed to check the accuracy of this procedure.

amounts[63] from decomposition of III; the amount of mesitoic acid in the mixture of decomposition products was determined by titration and the amount of benzaldehyde in the mixture was obtained from a uv absorbance–concentration plot prepared from authentic benzaldehyde λ_{max} 330 mμ in *n*-hexane.

The amount of mesityl phenyl diketone (V) in the above ethanol solution (25 ml) was determined by spectroscopic analysis using the peak at λ_{max} 400 mμ and an absorbance–concentration plot prepared from authentic V. The amount of V determined in this way was 18 mg (11% yield). For two further decompositions using 200 and 222 mg of III, 22 and 23 mg yields of V were obtained corresponding to 12 and 11% yields, respectively.

Oxidation of Benzyl Mesityl Ketone (II) to Mesityl Phenyl Diketone (V) during Attempted Methylation of Derived Bromo Grignard Reagent of II.—The derived bromo Grignard reagent of II (3.24 g, 7.80×10^{-3} mol) in anhydrous diethyl ether (50 ml) was placed in a round bottom flask equipped with stirrer, dropping funnel, and drying tube. Methyl iodide (2.28 g, 1.61×10^{-2} mol) was added with stirring. Anhydrous tetrahydrofuran (50 ml) was added to increase solubility of the derived Grignard reagent; diethyl ether was removed by distillation. More methyl iodide (2.28 g, 1.61×10^{-2} mol) was added. After standing overnight, ether (20 ml) and water (2 drops) were added. The reaction mixture was dried with anhydrous sodium sulfate and solvents were removed with a rotary evaporator. A reddish-brown oil remained from which yellow crystals of V deposited after standing for 2.5 days. V was recrystallized from methanol in 0.138 g yield (7.9%), mp 135–138°.[64] The ir spectrum[44] of V (Nujol mull) showed bands at 1661 (vs) and 1675 (sh, C=O), 1610 (s), 1595 (s), 851 (vs), 721 (s), and 699 cm^{-1} (m). V formed a mono-2,4-dinitrophenylhydrazone derivative which was recrystallized from 95% ethanol, mp 234–236° (lit.[14] 232–232.5°). The ir spectrum[44] of the mono-2,4-dinitrophenylhydrazone (Nujol) showed bands at 3275 (w), 1675 (s, C=O), 1612 (s), 1601 (s), 1510 (s), 1360 (s), 1308 (s), 920 (w), 912 (w), 848 (m), 843 (w), 740 (s), and 695 cm^{-1} (m).

Instruments and Measurements.—^1H nmr spectra were obtained with a Varian Associates DP-60 spectrometer. Tetramethylsilane was used as an internal standard. Chemical shifts were determined from side bands generated by a Hewlett–Packard wide range oscillator (Model 200 CDR) and calibrated against the chemical shift of neat acetaldehyde reported[65] as 455.7 ± 1.0 cps. Ir spectra were taken on Baird-Atomic (Model KM-1) and Perkin-Elmer (Model 337) spectrophotometers. Spectra were calibrated with bands from polystyrene film. Uv spectra were recorded with a Beckman DK-1 instrument. Vpc curves were obtained with a Wilkens Aerograph Model A-90 instrument using a silicone oil (GE-76) coated firebrick column.

The instrument for differential thermal analysis was similar to one designed by Stone.[66] The sample holder was constructed of high heat conductivity Inconel containing two holes, one for the sample and one for alumina which was used as inert reference material. Temperature differences between sample and reference were detected with a differential thermocouple of Pt–Pt + 10% Rh and recorded as a function of time. Samples were run as mixtures with alumina and also without added alumina. A Perkin-Elmer DSC-1B instrument was used for differential scanning calorimetry measurements. Temperatures were calibrated with an indium standard. Samples were sealed in aluminum capsules. An empty aluminum capsule was sealed and used as a reference.

Registry No.—3,3-Diphenyl-2-hydroperoxy-2′,4′,6′-trimethylpropiophenone, 25056-05-7; II, 1889-72-1; III, 25056-04-6; IV, 25056-06-8; V, 25056-07-9.

Acknowledgment.—The authors express appreciation to the Robert A. Welch Foundation of Houston, Texas, for research grants in support of this work.

(63) In an experiment performed in one of the earlier decompositions before the procedure was optimized, 33% mesitoic acid and 32% benzaldehyde were obtained. This decomposition was carried out using an oil bath at 200°, distilling the products *in vacuo* (*ca.* 1 mm). Volatile products were trapped at liquid air temperature, dissolved in *n*-hexane, and analyzed from absorption at 330 mμ for benzaldehyde. The residue was dissolved in ethanol, an equal volume of water was added, and the solution was titrated with standard sodium hydroxide for mesitoic acid.

(64) Mp 136–137° is reported[14] for material obtained from selenium dioxide oxidation of II.

(65) S. L. Manatt and D. D. Elleman, *J. Amer. Chem. Soc.*, **83**, 4095 (1961).

(66) R. D. Stone, The Ohio State University Studies, Eng. 20, No. 4, Eng. Expt. Sta. Bull. No. 146, 77, 1951. A full description is in C. C. Chou, Ph.D. Dissertation, Baylor University, 1968. The authors express appreciation to Professor J. L. McAtee, Jr., and Mr. C. C. Chou for use of the DTA equipment.

Photochemical Cycloadducts.[1] V.[2] Photochemical Addition of Olefins to the Steroidal 1-En-3-one System

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Steroidal 1-en-3-ones are surprisingly unreactive toward photocycloaddition with olefins. Ethylene, acetylene, 1,1-difluoroethylene, and maleic anhydride fail to add to a variety of 1-en-3-ones both under unsensitized and sensitized conditions at room temperature. 1,1-Dichloroethylene adds to 17β-acetoxy-5α-androst-1-en-3-one (**1**) to give the *trans* fused head-to-tail adduct (**2**). Vinyl acetate also adds to **1** to give both *trans* and *cis* fused head-to-tail adducts (**12**) and (**13a**). The structure and stereochemistry of these adducts are proved by chemical, spectroscopic, and X-ray crystallographic methods.

The steroidal 16-en-20-one system appears to undergo photochemical cycloaddition to the conjugated double bond very readily. Under mild conditions 3β-acetoxypregna-5,16-dien-20-one reacts with a variety of olefins, acetylene, and hexafluoroacetone to give 16,17-cyclobutanes, 16,17-cyclobutenes, and 16,17-oxetanes.[2,4] Likewise, the steroidal 4,6-dien-3-one system reacts readily, and photochemical cycloaddition products of 17β-acetoxyandrosta-4,6-dien-3-one with ethylene and with maleic anhydride have been isolated and characterized.[5]

Surprisingly, the steroidal 1-en-3-one system has proved to be much less reactive under the same conditions. Thus all attempts to add ethylene to the Δ^1 double bond of 17α,20:20,21-bismethylenedioxy-5α-pregn-1-en-3-one, 5α-androst-1-en-3-one, 17β-acetoxy-5α-androst-1-en-3-one, and 17β-acetoxy-2-methyl-5α-androst-1-en-3-one were unsuccessful. In each case ethylene was bubbled through a benzene or dioxane solution of the steroid, and the mixture was irradiated with a medium-pressure mercury lamp in water-cooled Pyrex apparatus for 2–18 hr. In all experiments, starting material was recovered in high yield and tlc examination of the reaction mixture showed no evidence of any addition product being formed. Negative results were also obtained when 17α,20:20,21-bismethylenedioxy-5α-pregn-1-en-3-one and 17β-acetoxy-2-methyl-5α-androst-1-en-3-one were irradiated with ethylene in dioxane solution in the presence of benzophenone. Attempts to add maleic anhydride to 17α,20:20,21-bismethylenedioxy-5α-pregn-1-en-3-one and to 17β-acetoxy-2-methyl-5α-androst-1-en-3-one by irradiation in dioxane solution, both in the presence and absence of benzophenone, also failed, as did attempted addition of acetylene to 17β-acetoxy-2-methyl-5α-androst-1-en-3-one in dioxane solution. Successful photocycloaddition to a 1-en-3-one steroid was finally achieved using unsymmetrical alkenes as addenda, and this paper described the addition of 1,1-dichloroethylene and of vinyl acetate to 17β-acetoxy-5α-androst-1-en-3-one (**1**).

Irradiation of benzene solution of **1** containing 1,1-dichloroethylene[6] afforded large amounts of a polymeric material derived from the olefin together with a mixture of steroidal products. Chromatographic separation of the latter gave 17β-acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (**2**) in 16% yield. The *trans* fusion of the cyclobutane ring in **2** was shown by equilibration with neutral alumina which gave the *cis* fused isomer **3a**. The same isomerization was effected by treating **2** with *p*-toluenesulfonic acid in benzene.

The nmr spectrum of **2** suggests that the two chlorine atoms are situated at position 1′. The 1 proton appears as a doublet at 2.58 ppm, J = 14 Hz, the 2′ protons as two overlapping quartets centered at 2.69 and 2.93 ppm, respectively, $J_{2',2'}$ = 12 Hz, $J_{2',2}$ = 7 and 9 Hz, and the 2 proton as a multiplet centered at 3.25 ppm. If the chlorine atoms were at position 2′, the same spin–spin coupling pattern would be expected, but the doublet would then be ascribable to the 2 H and this signal would be expected to appear downfield from the 1-H multiplet.

The 19-H resonance of **2** at 1.30 ppm is strongly deshielded relative to the 19-H signal of dihydrotestosterone acetate which occurs at 1.03 ppm. This suggests the 1β,2α stereochemistry for the cyclobutane ring in which the chlorine atoms are in the close proximity to the C-19 angular methyl group, rather than the alternative 1α,2β structure. On epimerization of **2** to the *cis* fused isomer **3a**, the 19-H resonance moves upfield to 1.10 ppm. This upfield shift is attributed to ring A of **3a** assuming a boat conformation, in which the C-19 angular methyl group lies partly within the shielding cone of the C-3 carbonyl group.

The argument for 1β,2α stereochemistry of **2** based on the downfield position of its 19-H resonance is not unequivocal. The nmr data are also compatible with 1α,2β stereochemistry for adduct **2**, if one assumes that the low-field position of the 19-H resonance is due to a transmitted electronegative effect of the two chlorine atoms. Although this effect would have to be transmitted through five σ bonds, it is known that a 9α-fluorine atom deshields the 19-H resonance by 0.133 ppm.[7] This ambiguity has been resolved by an X-ray

(1) Publication No. 368 from the Syntex Institute of Organic Chemistry.

(2) For part IV, see P. Sunder-Plassmann, P. H. Nelson, P. H. Boyle, A. Cruz, J. Iriarte, P. Crabbé, J. A. Zderic, J. A. Edwards, and J. H. Fried. *J. Org. Chem.*, **34**, 3779 (1969).

(3) Syntex Postdoctoral Fellow, 1966–1967, on leave of absence from Trinity College, Dublin.

(4) P. Sunder-Plassmann, P. H. Nelson, L. Durham, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.* 653 (1967); P. Sunder-Plassmann, J. Zderic, and J. H. Fried, *ibid.*, 3451 (1966).

(5) P. H. Nelson, J. W. Murphy, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **90**, 1307 (1968).

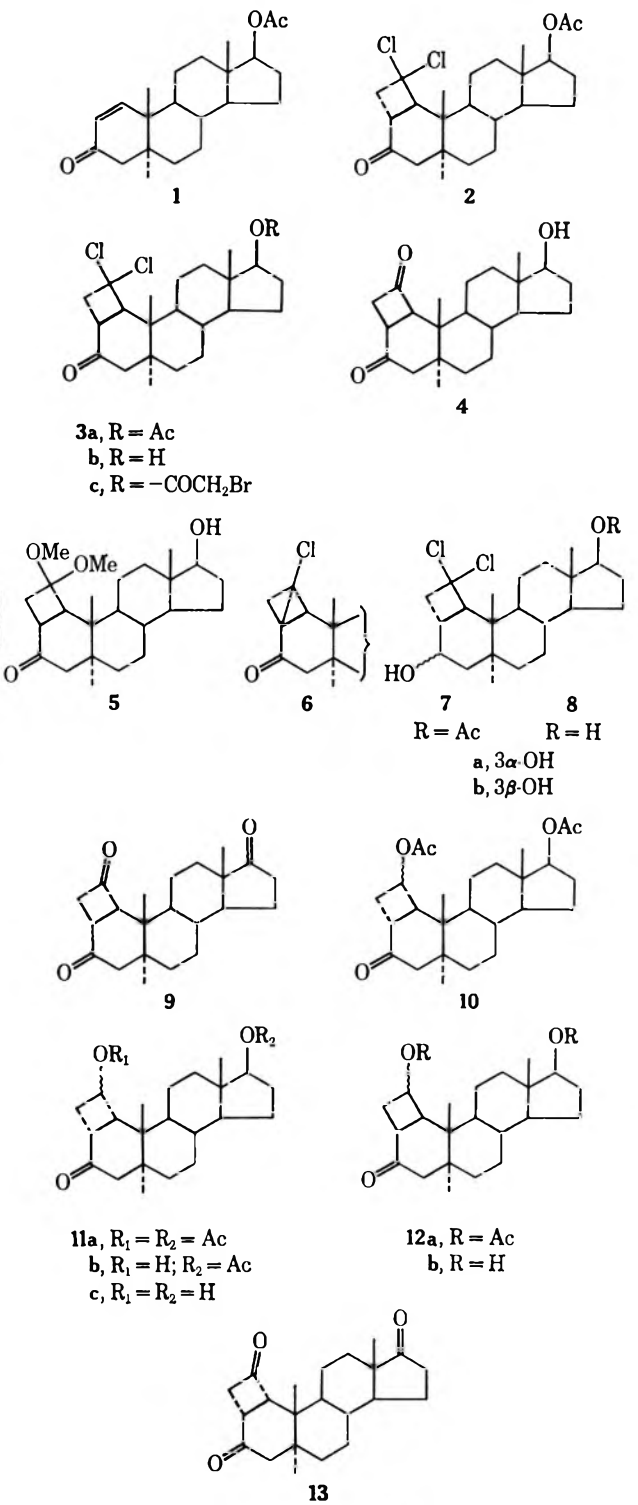
(6) While this work was in progress, O. L. Chapman described the photochemical addition of 1,1-dichloroethylene to isophorone to give the *cis*-fused 3′,3′-dichloroethylene adduct. See Abstracts of the 12th National Organic Symposium of the American Chemical Society Burlington, Vt., June 18–22, 1967, p. 118.

crystallographic analysis of the bromoacetate derivative **3c** kindly performed by Dr. Christensen of these laboratories. Dr. Christensen's results show that the cyclobutane ring of **3c** has the $1\beta,2\beta$ stereochemistry and the A ring exists in the boat conformation.[8] It follows that the initial adduct **2** must have $1\beta,2\alpha$ stereochemistry.

Treatment of adduct **2** with potassium hydroxide in aqueous dioxane afforded a mixture of products which on chromatography gave low yields of the *cis* fused 17β-alcohol **3b** and the cyclobutanone **4**. The latter showed a strong absorption in its infrared spectrum at 1775 cm^{-1}. A much more convenient route to the cyclobutanone **4** was achieved by refluxing either **3a** or **3b** in 1% methanolic potassium hydroxide when the dimethyl ketal **5** was obtained. This on hydrolysis with sulfuric acid in aqueous dioxane gave **4** in good yield. The ketal **5** could also be obtained directly from the *trans* fused adduct **2** by treatment with methanolic potassium hydroxide, when concomitant epimerization of C-2 and hydrolysis of the *gem*-dichloro group occurred. Compound **4** was oxidized with chromium trioxide in acetone to give the triketone **9**, showing three carbonyl bands at 1775, 1730, and 1705 cm^{-1} in its infrared spectrum. The hydrolysis of the *gem*-dichloro group in **3a** and **3b** by methanolic potassium hydroxide is of interest since this reaction is considered to proceed through the bicyclobutane intermediate **6**.[9] Indeed, the importance of the anionic center at C-2 for promoting hydrolysis of the *gem*-dichloro group is evident from methanolysis experiments conducted on the 3-hydroxy compounds **7a** and **7b**. Thus, boiling 1% methanolic potassium hydroxide smoothly transformed the latter substances into their respective diols, **8a** and **8b**, without affecting the *gem*-dichloro groupings.

The 3-hydroxy compounds, **7a** and **7b**, were obtained from **2** by hydrogenation over a platinum catalyst, the stereochemistry at C-3 being assigned on the basis of the chemical shift and the half band width of the 3-H signal[10] as well as the chemical shift of the 19-H signal.

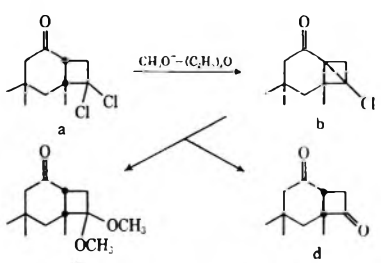
When **1** was irradiated with vinyl acetate[11] in benzene solution, a complex mixture of products was obtained. Column and preparative thin layer chromatography over silica gel effected a partial separation of the mixture and gave two pure products, **10** and **11a**, in low yields. The *trans*-cyclobutane ring fusion in **10** was demonstrated by equilibration on neutral alumina, when *cis* fused **12a** was obtained. The 19-H resonance of **10** shows an upfield shift of 0.23 ppm on this epimerization, suggesting that ring A in **12a** exists in the boat form. The $1\beta,2\alpha$ stereochemistry of **10** and also the position of the cyclobutane acetoxy group at C-1′ were established by hydrolysis of **10** to the corresponding diol **12b** (also obtained by hydrolysis of **12a**), followed by oxidation to a triketone which was identical in all respects with the triketone **9** obtained previously from



(7) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 21.

(8) Full details of the X-ray analysis will be reported elsewhere by Dr. A. Christensen.

(9) Chapman has shown that treatment of the bicyclic adduct (a) with sodium methoxide in ether yields the bicyclobutane (b) which is transformed by exposure to methanolic sodium methoxide and aqueous base into the dimethyl ketal (c) and the cyclobutanone (d), respectively. See ref 6.



(10) For examples illustrating the use of band width at half-height in determining the axial or equatorial orientation of an alicyclic methine proton, see A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964), and references cited therein.

(11) After the completion of this work the photochemical addition of vinyl acetate to the Δ^4-3 ketone system was reported: S. Terao, S. Tsushina, I. Agata, and T. Miki, *Kogyo Kagahu Zasshi*, **72**, 203 (1969).

the 1,1-dichloroethylene adduct **2**. The stereochemistry at C-1′ is unknown.

On treatment of the second photoadduct **11a** with neutral alumina, no trace of isomerized product could be detected, indicating the cyclobutane ring fusion to be *cis*. Hydrolysis of the adduct **11a** gave the diol **11c** which on oxidation gave a triketone **13**, showing three carbonyl bands at 1775, 1740, and 1700 cm^{-1} in its infrared spectrum, and a three-proton multiplet centered at 3.05 ppm together with a one-proton multiplet centered at 3.60 ppm in its nmr spectrum. Absence of a downfield doublet assignable to the 2-H proton precludes the alternative 2′-oxo structure. Since this triketone was different from the one previously obtained (**9**), it must have the 1α,2α stereochemistry as also must the initial adduct **11a**.

Although a complete product analysis was not undertaken, the present results are consistent with those of previous workers who have studied the photochemical addition of alkenes to α,β-unsaturated ketones. Thus, *trans* fusion of the cyclobutane ring in the photoadduct seems to be predominant.[11] Secondly, all of the 1,2 adducts are derived by addition of the carbon of the alkene bearing the electronegative substituent(s) to the β-carbon atom of the enone.[9,12,13] In the work of Miki and coworkers, however, describing some photoadducts of alkenes with testosterone acetate, both head-to-tail and head-to-head adducts are reported, and in some reactions the 4α,5α *cis* fused adducts were predominant.[11]

Despite the ready addition of both vinyl acetate and 1,1-dichloroethylene to 17β-acetoxy-5α-androst-1-en-3-one (**1**), neither of these alkenes reacts with 17β-acetoxy-2-methyl-5α-androst-1-en-3-one. This result agrees with Corey's observation that alkylation of C-2 of an enone is deleterious to the photochemical addition of an alkene.[12] 1,1-Difluorethylene, on the other hand, does not react even with **1**, another demonstration of the unreactivity of the steroidal 1-en-3-one system.

Experimental Section[14]

Irradiation Experiments.—All photolyses were conducted at 15–20° in Pyrex apparatus, using a 200-W Hanovia 654-A-36 medium-pressure mercury lamp as the source of ultraviolet light.

Photochemical Addition of 1,1-Dichloroethylene to 17β-Acetoxy-5α-androst-1-en-3-one (1).—A solution of **1** (6.0 g) and 1,1-dichloroethylene (40 ml) in benzene (75 ml) was irradiated for 4 hr. The reaction mixture was filtered to remove polymeric material and the vessel was cleaned. More 1,1-dichloroethylene (10 ml) was added and irradiation was continued. After a total irradiation period of 12.5 hr, the reaction mixture was filtered, the combined residues of polymeric material were washed with methylene dichloride, and the washings were added to the filtrate. Evaporation of solvent gave a viscous gum which partially dissolved on trituration with ether leaving a white solid residue (2.2 g). Chromatography on a column of silica gel (250 g), eluting with hexane–ethyl acetate (85:1), gave 17β-acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (**2**, 1.21 g, 16% yield): mp 253°; $[\alpha]_D$ +54°; ν_{max} 1725, 1720, 1240 cm^{-1}; nmr (100 Mc) 0.83 (s, 18-H), 1.30 (s, 19-H), 2.02 (s, 17β-acetoxy H), 2.58 (d, $J_{1,2}$ = 14 Hz, 1-H), 2.69 (q, $J_{2',2'}$ = 12, $J_{2,2'}$ = 7 Hz, 2′ H), 2.93 (q, $J_{2',2'}$ = 12, $J_{2,2'}$ = 9 Hz, 2′-H), 3.25 (m, 2-H), 4.60 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{32}O_3Cl_2$: C, 64.63; H, 7.54; Cl, 16.59. Found: C, 64.72; H, 7.70; Cl, 16.47.

Conversion of 1β,2α Adduct (2) into the 1β,2β Adduct (3a). (a) **With *p*-Toluenesulfonic Acid.**—A solution of **2** (0.89 g) and *p*-toluenesulfonic acid monohydrate (0.15 g) in benzene (110 ml) was refluxed for 16 hr. The solution was cooled, washed with aqueous sodium carbonate and water, dried ($MgSO_4$), and evaporated, yielding a clear oil (0.89 g) which solidified on standing. Chromatography on a column of silica gel (60 g), eluting with hexane–ethyl acetate (17:3) afforded 17β-acetoxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (**3a**): mp 220°; $[\alpha]_D$ +93°; ν_{max} 1730, 1715, 1245 cm^{-1}; nmr (100 Mc) 0.80 (s, 18-H), 1.10 (s, 19-H), 2.03 (s, 17β-acetoxy H), 3.1–3.7 (complex spin pattern, four protons, 1-H, 2-H, 2′-H), 4.60 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{32}O_3Cl_2$: C, 64.63; H, 7.54; Cl, 16.59. Found: C, 64.64; H, 7.48; Cl, 16.76.

(b) **With Alumina.**—A solution of **2** (0.27 g) in ethyl acetate (40 ml) and chloroform (10 ml) was stirred with neutral alumina (27 g, Woelm activity grade I) for 5.75 hr. The residue obtained after removal of alumina and evaporation of solvent was chromatographed on preparative tlc plates (hexane–ethyl acetate, 3:1) to give starting material **2** and **3a** identical with the product obtained above.

17β-Hydroxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (3b).—A solution of 17β-acetoxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (**3a**, 0.76 g) and *p*-toluenesulfonic acid monohydrate (0.76 g) in methanol (100 ml) was refluxed for 6 hr. The reaction mixture was diluted with benzene (200 ml) and the resulting solution was washed with water, aqueous sodium carbonate solution, and water, dried ($MgSO_4$), and evaporated. The residual yellow oil was dissolved in benzene–methylene dichloride. Addition of hexane precipitated a solid which on crystallization from ethyl acetate gave white crystals of the 17-alcohol (**3b**): mp 204–205°; ν_{max} 3550, 1700 cm^{-1}; nmr (100 Mc) 0.76 (s, 18-H), 1.11 (s, 19-H), 1.55 (broad s, disappeared on addition of D_2O, –OH), 3.20–3.75 ppm (complex spin pattern, five protons, 17α-H, 1-H, 2-H, 2′-H); mass spectrum *m/e* 384 (M^+ for ^{35}Cl), 386 (M^+ for ^{37}Cl).

17β-Bromoacetoxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (3c).—A methylene dichloride solution of 17β-hydroxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (**3b**, 0.210 g) was treated with 1.5 mol α-bromoacetyl bromide and then with 1.5 mol of pyridine, both in methylene dichloride at room temperature for 72 hr. The reaction mixture was washed with water, dried ($MgSO_4$), and evaporated. Chromatography of the residue on a column of silica gel (30 g), eluting with hexane–ethyl acetate (9:1), gave crystals of the 17β-bromoacetate (**3c**, 0.19 g): mp 181–182°; ν_{max} 1725, 1705 cm^{-1}; nmr (60 Mc) 0.83 (s, 18-H), 1.09 (s, 19-H), 3.78 (s, $-COCH_2$-Br), 4.65 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{31}O_3BrCl_2$: C, 54.54; H, 6.17. Found: C, 54.45; H, 6.13.

Treatment of 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (2) with Potassium Hydroxide in Dioxane.—Potassium hydroxide (2.0 g) in water (10 ml) was added to a solution of **2** (0.76 g) in dioxane (150 ml). A clear oil separated and the mixture was stirred at 90° for 3 hr, when it was poured into water and neutralized with sulfuric acid. The clear yellow solution was extracted with ethyl acetate and the extract was washed with water, dried ($MgSO_4$), and evaporated, giving a yellow solid (0.64 g). This was chromatographed on a column of silica gel (60 g), eluting first with hexane and finally with hexane–ethyl acetate (2:1) using a continuous solvent gradient technique. Two main products were isolated: 17β-hydroxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (**3b**, 85 mg, least polar), identical with **3b** described above, and 17β-hydroxy-1β,2β-ethyl-

(12) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964).

(13) J. W. Hanifin and E. Cohen, *Tetrahedron Lett.*, 5421 (1966); N. C. Yang, *Pure Appl. Chem.*, **9**, 591 (1964).

(14) Melting points are corrected and were taken on a Fisher-Johns apparatus or a Thomas–Hoover capillary apparatus. Optical rotations were measured in dioxane solution at 27° and infrared spectra were determined in KBr disks unless otherwise specified. Ultraviolet spectra were measured on a Cary Model 14 spectrometer. We wish to thank Dr. L. Throop and his staff for these measurements. Nmr spectra were recorded for 5–10% solutions (w/v) in deuteriochloroform containing tetramethylsilane as internal reference on Varian A-60 and HA-100 spectrometers. Chemical shifts are reported as parts per million on the δ scale to the nearest 0.01 ppm. Coupling constants are in cycles per second to the nearest 0.5 Hz. We thank Mr. J. W. Murphy and Miss J. Tremble for assistance with these measurements. In the presentation of data, s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were obtained with an Atlaswerke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionizing potential of 70 eV and an acceleration voltage of 3 kV. We wish to thank Dr. L. Tökes and Mr. J. Smith for assistance with these measurements. Microanalyses were performed by Dr. A. Bernhardt, Mülheim (Ruhr), West Germany. Tlc plates with a thickness of 0.25-mm silica gel GF_{254} (E. Merck AG Darmstadt) were used.

ene-5α-androstane-1′,3-dione (**4**, 25 mg, most polar), which had mp 194–195°; ν_{max} 3300, 1775, 1705 cm^{-1}; nmr (100 Mc) 0.75 (s, six protons, 18-H, 19-H), 1.55 (broad s, disappeared on addition of D_2O, –OH), 3.0–3.3, 3.5–3.8 ppm (complex pattern, five protons, 1-H, 2-H, 2′-H, 17α-H). *Anal.* Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.91; H, 9.20.

17β-Hydroxy-1β,2β-(1′,1′-dimethoxyethylene)-5α-androstan-3-one (5).—A solution of 17β-acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (**2**, 0.37 g) in 1% methanolic potassium hydroxide was refluxed for 1.5 hr. The solution was concentrated to half its volume and poured into ice water (300 ml). Crystallization of the precipitated solid from methanol gave **5** (0.20 g): mp 156–157° (the compound melted and resolidified at 95–100°); $[\alpha]_D$ +95°; ν_{max} 1705, 1695 cm^{-1} (KBr), 3620, 1700 cm^{-1} ($CHCl_3$); nmr (60 Mc) 0.77 (s, 18-H), 0.90 (s, 19-H), 1.77 (s, disappeared on addition of D_2O, –OH), 3.12, 3.20 (two s, –OMe), 3.6 ppm (m, 17α-H), mass spectrum *m/e* 376 (M^+). This product partially decomposed on repeated crystallization and an analytically pure sample could not be obtained.

Treatment of **3a** or **3b** with 1% methanolic potassium hydroxide as described above also yielded the dimethyl ketal **5**.

17β-Hydroxy-1β,2β-ethylene-5α-androstane-1′,3-dione (4).—A solution of 17β-hydroxy-1β,2β-(1′,1′-dimethoxyethylene)-5α-androstan-3-one (**5**, 90 mg) in dioxane (2.2 ml) and water (2 ml) containing 1 drop of 50% sulfuric acid was heated at 100° for 0.75 hr. After cooling, the reaction mixture was diluted with ethyl acetate and the solution was washed with water, dried ($MgSO_4$), and evaporated, giving dione **4** (44 mg), identical with the product already described.

1β,2β-Ethylene-5α-androstane-1′,3,17-trione (9).—An excess of Jones reagent (2 ml) was added to a solution of 17β-hydroxy-1β,2β-ethylene-5α-androstane-1′,3-dione (**4**, 30 mg) in acetone (5 ml). After allowing the mixture to stand at room temperature for 15 min, it was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated, yielding a solid (25 mg) which on crystallization from hexane–ethyl acetate gave white crystals of the triketone **9**: mp 246–248°; $[\alpha]_D$ +156°; ν_{max} 1775, 1730, 1705 cm^{-1}; nmr (100 Mc) 0.77 (s, 19-H), 0.88 (s, 18-H), 3.0–3.8 ppm (complex spin pattern, four protons, 1-H, 2-H, 2′-H). *Anal.* Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.72; H, 8.41.

Hydrogenation of 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (2).—A suspension of anhydrous sodium acetate (0.38 g) and 5% platinum-on-carbon catalyst (0.57 g) in a solution of **2** (1.13 g) in ethyl acetate (200 ml) was hydrogenated at atmospheric temperature and pressure until uptake of hydrogen ceased. Filtration and evaporation of the reaction mixture gave a white solid (1.08 g) which was chromatographed on a column of silica gel (100 g), eluting with hexane–ethyl acetate (4:1). 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3α-ol (**7a**, 0.50 g) was eluted first: mp 208°; $[\alpha]_D$ +42°; ν_{max} 3450, 1715, 1275 cm^{-1}; nmr (60 Mc) 0.81 (s, 18-H), 1.09 (s, 19-H), 1.77 (s, disappeared on addition of D_2O, –OH), 2.01 (s, 17β-acetoxy-H), 4.02 (broad s, $W_{1/2}$ = 6 Hz, 3β-H), 4.60 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{34}O_3Cl_2$: C, 64.33; H, 7.98; Cl, 16.51. Found: C, 74.06; H, 8.16; Cl, 16.70. 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3β-ol (**7b**, 0.50 g) was eluted next: mp 231°; $[\alpha]_D$ +8°; ν_{max} 3620, 1720 cm^{-1} ($CHCl_3$); nmr (60 Mc) 0.82 (18-H), 1.13 (19-H), 1.80 (s, disappeared on addition of D_2O, –OH), 2.03 (s, 17β-acetoxy H), 3.60 (m, $W_{1/2}$ = *ca.* 17 Hz, 3α-H), 4.60 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{34}O_3Cl_2$: C, 64.33; H, 7.98; Cl, 16.51. Found: C, 64.20; H, 8.08; Cl, 16.63.

Hydrolysis of 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3α-ol (7a).—A solution of **7a** (0.15 g) in 1% methanolic potassium hydroxide (25 ml) was refluxed for 1.5 hr. The solution was poured into water (75 ml) and the mixture was extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated, giving a white solid (0.15 g). Crystallization from hexane–ethyl acetate afforded pure 3α,17β-diol **8a**: mp 203°; $[\alpha]_D$ +46°; ν_{max} 3625, 3460 cm^{-1} ($CHCl_3$). *Anal.* Calcd for $C_{21}H_{32}O_2Cl_2$: C, 65.11; H, 8.33; Cl, 18.31. Found: C, 64.84; H, 8.46; Cl, 18.13; mass spectrum, *m/e* 386, 388 (m^+). Similar hydrolysis of **7b** gave 3β,17β-diol **8b**: mp 217–220°; $[\alpha]_D$ +22°; ν_{max} 3350 cm^{-1} (Nujol). *Anal.* Calcd for $C_{21}H_{32}O_2Cl_2$: Cl, 18.31. Found: Cl, 17.83 mass spectrum, *m/e* 386, 388 (M^+).

Photochemical Addition of Vinyl Acetate to 17β-Acetoxy-5α-androst-1-en-3-one (1).—A solution of **1** (1.56 g) in vinyl acetate (47 ml) and benzene (20 ml) was irradiated for 13 hr. Evaporation of the solvent gave a clear viscous oil which was chromatographed on a column of silica gel (285 g), eluting with hexane–ethyl acetate (solvent composition changed gradually from 83:17 to 50:50, using a continuous solvent gradient technique) and collecting 20-ml fractions. Fractions 86–99 contained two main components (tlc) and these were separated by preparative tlc (hexane–ethyl acetate 85:15, each plate run nine successive times). The product of greatest R_f proved to be starting material **1** (7 mg). The other product was 17β-acetoxy-1α,2α-(1′ξ-acetoxyethylene)-5α-androstan-3-one (**11a**, 32 mg, 2% yield): mp 168°; $[\alpha]_D$ +12°; ν_{max} 1730, 1700 cm^{-1}; nmr (100 Mc) 0.80 (s, 18-H), 0.96 (s, 19-H), 1.98, 2.02 (two s, acetoxy H), 2.4–3.0 (complex pattern), 4.58 (m, 17α-H), 5.10 ppm (m, 1′-H). *Anal.* Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.22; H, 8.79. Fractions 106–152 were combined and evaporated, affording a gum which contained three principal components (tlc). The gum was triturated with hexane–ethyl acetate, giving a white solid which on crystallization from hexane–ethyl acetate gave pure 17β-acetoxy-1β,2α-(1′ξ-acetoxyethylene)-5α-androstan-3-one (**10**, 0.17 g, 9% yield): mp 202–205°; $[\alpha]_D$ +65°; ν_{max} 1735, 1725, 1715, 1255 cm^{-1}; nmr (100 Mc) 0.79 (s, 18-H), 1.03 (s, 19-H), 1.97 (s, 1′-acetoxy H), 2.01 (s, 17β-acetoxy H), 4.5–4.9 ppm (m, two protons, 17α-H, 1′-H). *Anal.* Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.10; H, 8.79.

17β-Acetoxy-1β,2β-(1′ξ-acetoxyethylene)-5α-androstan-3-one (12a).—A solution of **10** (0.24 g) in ether (95 ml) and ethyl acetate (5 ml) at 20° was stirred with neutral alumina (24 g, Woelm activity grade I) for 0.75 hr. Filtration followed by evaporation of solvent gave a white solid (0.24 g). Crystallization from hexane–ethyl acetate gave **12a**: mp 165°; $[\alpha]_D$ +45°; ν_{max} 1730, 1720 cm^{-1}; nmr (100 Mc) 0.76 (s, 18-H), 0.80 (s, 19-H), 2.00, 2.03 (two s, acetoxy H), 2.6–3.1 (complex pattern, three protons), 4.65 (m, 17α-H), 5.02 ppm (m, 1′-H). *Anal.* Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.61; H, 8.68.

17β-Hydroxy-1β,2β-(1′ξ-hydroxyethylene)-5α-androstan-3-one (12b).—A solution of 17β-acetoxy-1β,2α-(1′ξ-acetoxyethylene)-5α-androst-3-one (**10**, 0.126 g) and potassium hydroxide (2.0 g) in methanol (100 ml) and water (2 ml) was allowed to stand at 20° for 5 hr. The mixture was poured into water (250 ml) and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The white solid residue (0.08 g) was crystallized from hexane–ethyl acetate giving the 1′ξ,17β-diol (**12b**): mp 198°; $[\alpha]_D$ +107°; ν_{max} 3300, 1700 cm^{-1} (Nujol); nmr 0.72 (s, 18-H), 0.77 (s, 19-H), 3.62 (m, 17α-H), 4.05 ppm (m, 1′-H). *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.67; H, 9.85. **12b** was also obtained by similar hydrolysis of 1′ξ,17β-diacetate (**12a**).

Oxidation of 17β-Hydroxy-1β,2β-(1′ξ-hydroxyethylene)-5α-androstan-3-one (12b).—Oxidation of **12b** with chromium trioxide in acetone yielded a triketone identical in spectra, tlc, and mixture melting point with triketone **9** already described.

Treatment of 17β-Acetoxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (11a) with Alumina.—A solution of **11a** (99 mg) in dry ether (55 ml) was stirred with neutral alumina (8.1 g, Woelm activity grade I) at 20° for 5 hr. The alumina was filtered off and washed with ethyl acetate and then with methylene dichloride. Evaporation of the combined solutions gave a white solid (63 mg). This was separated into two components by preparative tlc (hexane–ethyl acetate, 40:60). The less polar product (23 mg) was identical (melting point, mixture melting point, ir, nmr, tlc) with the starting material. The more polar product (15 mg) was probably 17β-acetoxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (**11b**): nmr (60 Mc) 0.78 (s, 18-H), 0.93 (s, 19-H), 1.98 (s, 17β-acetoxy H), 4.08 (m, 1′-H), 4.53 ppm (m, 17α-H).

17β-Hydroxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (11c).—A solution of 17β-acetoxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (**11a**, 0.21 g) and potassium hydroxide (2.3 g) in methanol (115 ml) and water (2.3 ml) was allowed to stand at room temperature for 6 hr. The solution was then poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated. Crystallization of the residue (0.17 g) from aqueous ethanol gave white needles of 1′ξ,17β-diol (**11c**): mp 115–116°; $[\alpha]_D$ –3°; ν_{max} 3450, 1700 cm^{-1} ($CHCl_3$); nmr (60 Mc) 0.75 (s, 18-H), 0.97 (s, 19-H), 3.5–4.2 ppm (m, 1′-H and 17α-H). *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.08; H, 9.98.

1α,2α-Ethylene-5α-androstane-1′,3,17-trione (13).—17β-Hydroxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (**11c**, 45 mg) was dissolved in acetone (5 ml) and excess Jones reagent was added. After allowing the mixture to stand at 20° for 15 min, it was poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated, yielding a white solid (34 mg) which on crystallization from hexane–ethyl acetate gave 1′,3,17-trione (**13**): mp 207°; $[\alpha]_D$ +86° ($CHCl_3$); ν_{max} 1775, 1735, 1700 cm^{-1} ($CHCl_3$); nmr (100 Mc) 0.86 (s, 18-H), 0.89 (s, 19-H), 2.7–3.4 (m, three protons), 3.45–3.75 ppm (m, one proton). *Anal.* Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.21; H, 8.41.

Registry No.—**2**, 24467-63-8; **3a**, 24515-46-6; **3b**, 24467-64-9; **3c**, 24467-65-0; **4**, 24467-66-1; **5**, 24467-67-2; **7a**, 24467-68-3; **7b**, 24467-69-4; **8a**, 24467-70-7; **8b**, 24467-71-8; **9**, 24515-47-7; **10**, 24523-22-6; **11a**, 24467-72-9; **11b**, 24467-73-0; **11c**, 24515-48-8; **12a**, 24467-74-1; **12b**, 24471-11-2; **13**, 24471-12-3.

Synthetic Approaches to Some of the *Lythraceae* Alkaloids[1]

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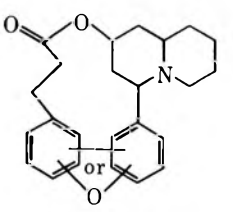
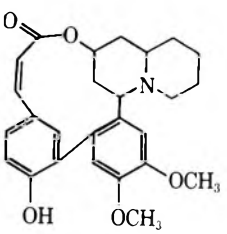
The uncoupled precursor (**20**) to dihydrolyfoline (**22**), a *Lythraceae* alkaloid was prepared by a biogenetic-type synthesis, based upon the assumption that the alkaloids arise from phenylpropane, acetate, and/or lysine sources. Condensation of the acryloylacetic ester (**12**) with Δ^1-piperideine (**7**) gave 1-carbethoxy-2-keto-4-(3-benzyloxy-4-methoxyphenyl)-*trans*-quinolizidine (**13**). Decarboxylation of **13** and reduction of the tetraphenylborate salt of the resulting ketone (**14**) with $NaBH_4$ gave a mixture of alcohols from which the axial isomer (**16**) was separated. Esterification of the alcohol (**16**) with *p*-benzyloxyhydrocinnamic acid and debenzylation yielded the desired compound (**20**). Preliminary attempts to couple **20** oxidatively to provide dihydrolyfoline (**22**) or another of the *Lythraceae* alkaloids have failed.

The alkaloids of the genera *Heimia* and *Decodon*, family *Lythraceae*, are a series of about 17 compounds corresponding to **1**. These alkaloids[2] contain a quinolizidine ring bearing phenyl and phenylpropionyloxy substituents. The two benzene rings are joined either by a biphenyl or a biphenyl–ether bridge. The structures of the alkaloids are based upon chemical correlations[3] with lythrine (**2**) and vertaline (**3**), whose structures were solved by X-ray analysis.[4]

Experimental data about the biosynthesis of these compounds was not available when this investigation was initiated.[5] Therefore, it was necessary for us to suggest a plausible route by which they might be formed *in vivo*. For the purpose of discussion, the molecules may be divided into cinnamate and 4-phenylquinolizidine portions. Considering the type and the oxygenation patterns of the phenyl–phenyl system, it seems logical to believe that these alkaloids are formed by an oxidative phenol coupling of the two portions.[6] Whether the phenyl–phenyl connection is made before or after the ester formation is debatable.



1



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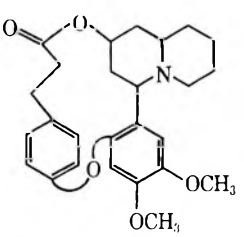

3

It has been suggested[7] without experimental data that the quinolizidine ring system (**5**) could arise from isopelletierine (**4**) and a suitably substituted benzaldehyde as shown in Scheme I. This approach was used[8] for the preparation of a mixture of *cis*- and *trans*-4-phenyl-2-ketoquinolizidines (**5** with no substituents) which was reduced to give a mixture of the epimeric alcohols. No reactions have been reported with oxygenated quinolizidines.

It would seem equally logical that the quinolizidine system might arise from a suitable phenyl–polyketide precursor such as **6** and Δ^1-piperideine (**7**). We would like to report the application of this approach in the synthesis of these alkaloids. The original plan was to prepare the uncoupled precursor (**20**) to the alkaloids and oxidize it to form the phenyl–phenyl connection to yield dihydrolyfoline (**22**). Compound **20** was prepared as

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(2) (a) J. P. Ferris, *J. Org. Chem.*, **27**, 2985 (1962); **28**, 817 (1963); (b) R. N. Blomster, A. E. Schwarting, and J. M. Bobbitt, *Lloydia*, **27**, 15 (1964); (c) H. Appel, A. Rother, and A. E. Schwarting, *ibid.* **28**, 84 (1965).

(3) (a) A. Rother H. Appel, J. M. Kiely, A. E. Schwarting, and J. M. Bobbitt, *ibid.*, **28**, 90 (1965); (b) J. P. Ferris, C. B. Boyce, R. C. Briner, B. Douglas, J. L. Kirkpatrick, and J. A. Weisbach, *Tetrahedron Lett.*, 3641 (1966).

(4) (a) D. E. Zaccharias, C. A. Jeffrey, B. Douglas, J. A. Weisbach, J. L. Kirkpatrick, J. P. Ferris, C. B. Boyce, and R. C. Briner, *Experientia*, **21**, 247 (1965); (b) S. C. Chu, G. A. Jeffrey, B. Douglas, J. L. Kirkpatrick, and J. A. Weisbach, *Chem. Ind.* (London), 1795 (1966); (c) J. P. Ferris, R. C. Briner, C. B. Boyce, and M. J. Wolf, *Tetrahedron Lett.*, 5125 (1966); (d) D. A. Hamilton and L. K. Steinrauf, *ibid.*, 5123 (1966).

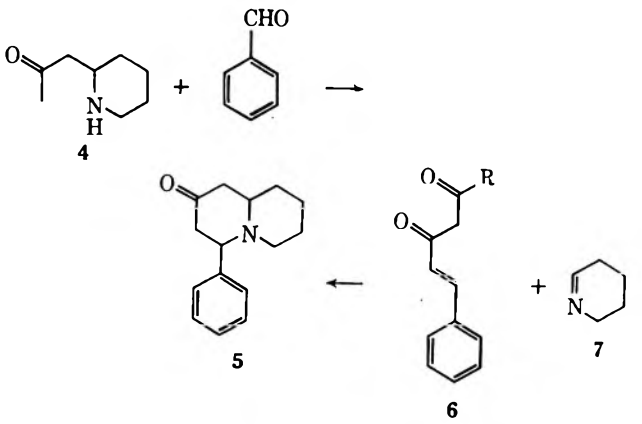
(5) Phenylalanine has since been shown to be a precursor of the phenylcinnamoyl moiety of one of the *Heimia* alkaloids. See A. Rother and A. E. Schwarting, *Chem. Commun.*, 1411 (1969).

(6) A. R. Battersby in "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 119.

(7) J. P. Ferris, C. B. Boyce, and R. C. Briner, *Tetrahedron Lett.*, 5129 (1966).

(8) T. Matsunaga, I. Kavasaki, and T. Kaneko, *ibid.*, 2471 (1967).

SCHEME I



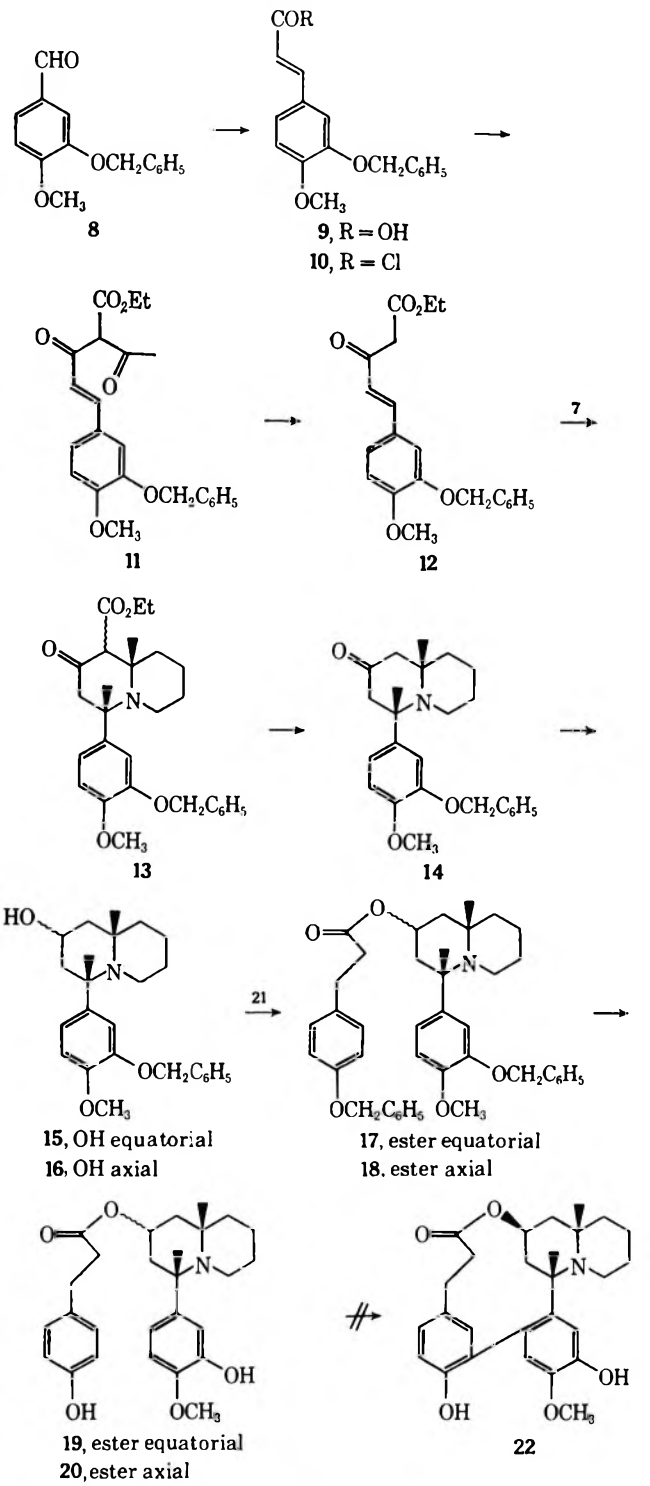
described in Scheme II, but the oxidation has not yet been successful.

Benzylisovanillin (**8**)[9] was allowed to react with malonic acid to yield the cinnamic acid (**9**).[10] Although the melting point of **9** was not in agreement with the literature, the structure was shown to be correct by nmr, microanalysis, titration, and reduction to the known 3-hydroxy-4-methoxyhydrocinnamic acid.[11] The acid chloride (**10**) was prepared with thionyl chloride in xylene and allowed to react with sodium ethylacetoacetate to yield **11**. A modification of the procedure of English and Lapides[12] was used. Compound **11** is yellow and its ir spectrum contains only a single carbonyl peak, both properties probably due to its highly enolic character (positive $FeCl_3$ test). The ester (**11**) was deacylated with ammonia in xylene to yield **12** by a modification of the procedure of Guha and Nasipuri.[13] Like **11**, **12** probably exists largely in the enolic form. The nmr spectra of compounds **8** to **12** were in agreement with the structures.

Δ^1-Piperideine (**7**) is a difficult compound to prepare. It may exist in any one of three trimeric forms,[14] α-, β-, and isotripiperideine. Only the α and β forms depolymerize to form **7**. The mixture of isomers prepared according to the literature[14] yielded the α form only when seeded with an authentic sample;[15] otherwise, the useless iso form crystallized.

The condensation of **7** with **12** to form the quinolizidine **13** is somewhat similar to the methods used by Lions and Willison to prepare indolizidines,[16] and by Anet, Hughes, and Ritchie[17] for the preparation of quinolizidines. In both cases, the portion similar to **12** was formed in the reaction mixture from ethyl acetonedicarboxylate and an aldehyde, and in neither case was the reaction very satisfactory. A more recent example[18] involves the condensation of α,β-unsaturated ketones

SCHEME II



with unsaturated λ-carbolines to yield indoloquinolizidones.

The condensation of **7** and **12** was found to take place in neutral solution (in contrast to the previous work which required slightly acidic media[16-18]) to give **13** in high yield (84%). The stereochemistry of **13** is based upon the reasoning that a structure with the benzene ring in the equatorial position would be the most stable and on the presence of Bohlmann bands[19] in its ir spectrum. These bands are said to be due to an interaction between the electron pair on the nitrogen and the axial

(9) A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 817 (1930).
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(11) M. B. Moore, H. B. Wright, M. Vernsten, M. Freifelder, and B. K. Richards, *J. Amer. Chem. Soc.*, **76**, 3656 (1954).
(12) J. English, Jr., and L. J. Lapides, *ibid.*, **65**, 2466 (1943).
(13) M. Guha and D. Nasipuri, *Org. Syn.*, **42**, 41 (1962).
(14) C. Schöpf, G. Berry, F. Braun, H. Hinkel, and R. Rakahl, *Justus Liebigs Ann. Chem.*, **559**, 1 (1948).
(15) M. M. El-Olemy and A. E. Schwarting, *J. Org. Chem.*, **34**, 1352 (1969).
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(17) E. F. L. J. Anet, G. H. Hughes, and A. Ritchie, *Aust. J. Sci. Res.*, **3A**, 635 (1950).
(18) C. Szantay, L. Töke, K. Hantz, and G. Kalaus, *J. Org. Chem.*, **32**, 432 (1967).
(19) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

hydrogens α to the nitrogen.[20] The ir spectrum of **13** showed two carbonyl groups, and the nmr and mass spectra could be correlated with the structure. All of the compounds after **13** are racemic.

Saponification and decarboxylation of **13** to yield **14** took place in dilute base, rather than in the usual base followed by acid reaction. Attempts to carry out the normal saponification and acid decarboxylation gave **14** in low yield. It was found that the yields were quite independent of the time that the acidic mixture was heated but somewhat dependent upon the time of base treatment. A systematic study of yield *vs.* concentration of KOH in ethanol–water (1:1) showed that a maximum yield (55%) could be obtained in 0.5% base. Yields fell off sharply below 0.25% and above 1% KOH. When the base required for the saponification was subtracted from the total base present, the KOH concentration dropped to 0.1%. Thus, the reaction takes place in an extremely dilute basic medium. The necessity of using dilute base for the saponification can be rationalized by the reversible character of the reaction used to form **13**, but the dependence of the decarboxylation upon base concentration is not entirely clear. It is interesting to note that all attempts to decarboxylate the ester of 4-phenyl-2-ketoquinolizidine-1,3-dicarboxylate failed.[17] The structure of **14** was in complete agreement with its ir, nmr, and mass spectra.

The reduction of **14** to the epimeric alcohols **15** and **16** also required extensive exploratory work. The reduction of such 2-ketoquinolizidines usually[8,21] leads to the formation of a mixture of epimers in which the equatorial isomer predominates by about 10:1. Unfortunately, for our purposes it was necessary to produce the axial isomer **16**. Catalytic hydrogenation gave poor overall yields of alcohol with platinum, palladium on carbon, and ruthenium on carbon (reported[21] to give the highest yields of axial alcohols). Reductions with $NaBH_4$ and $LiAlH_4$ gave good overall yields, but, as expected,[21] the equatorial isomer was the major component. For tenuous theoretical reasons, it was decided to carry out the reductions with $NaBH_4$ on complexed forms of the quinolizidine. Consequently, the reactions were carried out on complexes prepared in methanol with $AlCl_3$, $AlBr_3$, AlI_3, and sodium tetraphenylborate.[22] The axial:equatorial ratios, as estimated from comparative tlc follow: uncomplexed, 1:10, $AlCl_3$, decomposed; $AlBr_3$, 1:4; AlI_3, 3:7; and sodium tetraphenylborate, 1:1. The borate reaction was carried out in quantity and 40% of the axial isomer was isolated. The overall yields of the alcohol mixture were excellent. Several explanations are possible for this shift in the ratios, but none is especially satisfying, and none has been proved. There does appear to be a steric effect. It is possible that complexing destroys the original stereospecific reduction, thus producing a more random isomer distribution.

The structures of the two epimers, **15** and **16**, are based upon the following: first, the well-known fact that the equatorial isomer predominates[8,21,23] under normal hydride reductions; second, the chemical shift of the carbinol carbon proton of the alcohols. These have been assigned[8,24] as τ 6.02 and 6.53 for the axial and equatorial compounds, respectively. The values for **16** and **15** were τ 5.88 and 6.49. Both structures were in accord with their ir, nmr, and mass spectra in all respects. The axial isomer only was crystalline.

The two alcohols, **15** and **16**, were separately converted to their respective esters **17** and **18**, by transesterification[25] with methyl-*p*-benzyloxyhydrocinnamate (**21**) in xylene and methoxide. Compound **21** was prepared from *p*-benzyloxyhydrocinnamic acid[26] through the acid chloride. It was later learned that the esters **17** and **18** were easier to separate than the alcohols **15** and **16**. In the preparative procedures, the alcohol mixture was transesterified, and the epimeric esters were separated by column chromatography. Only the axial isomer **18** could be crystallized. The structures of these compounds were in accord with their spectra.

Debenzylation of **17** and **18** with hydrogen and palladium on carbon took place quantitatively to yield the diphenols, **19** and **20**. Neither of these compounds could be crystallized. The structures were in accord with their spectra.

Attempts to couple the diphenols oxidatively to any of the desired products (**1**) using $FeCl_3$,[27] $K_3Fe(CN)_6$,[27] electrolytic oxidation,[28] and catalytic oxygenation[29] failed to yield any recognizable products.

Experimental Section[30]

3-Benzyloxy-4-methoxycinnamic Acid (9).—A solution of malonic acid (24 g, 0.231 mol), benzylisovanillin[9] (**8**) (25 g, 0.103 mol), and piperidine (1 ml) in 55 ml of dry pyridine was stirred at 90° for 3 hr, and then at reflux for 2 hr. While hot, the solution was poured onto 200 ml of water and ice. After 1 hr, the precipitated solid was collected by filtration, washed (H_2O), air-dried, and crystallized from absolute ethanol to give 25.3 g (86%) of **9** as fine white needles: mp 214–216° (lit.[9] mp 179–180°); nmr (NaOD) τ 3.33 (m, 10, aromatic and vinylic), 6.62 (s, 3, OCH_3).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67; neut equiv, 284. Found: C, 72.39; H, 5.89; neut equiv, 290.

Compound **9** was catalytically hydrogenated over Pd–C to yield 3-hydroxy-4-methoxyhydrocinnamic acid, mp 146° (lit.[11] mp 146°).

Ethyl 2-Acetyl-3-keto-5-(3-benzyloxy-4-methoxyphenyl)-4-pentenoate (11).—A mixture of **9** (19 g, 0.067 mol, dried at 110° for 12 hr) and $SOCl_2$ (15.8 g, 0.134 mol) in 100 ml of dry xylene

(20) H. P. Hamlow and S. Okuda, *Tetrahedron Lett.*, 2553 (1964).

(21) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

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(23) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 30.

(24) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).

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(26) D. G. Doherty, *J. Amer. Chem. Soc.*, **77**, 4887 (1955).

(27) H. Musso in ref 7, p 1.

(28) G. F. Kirkbright, J. T. Stock, R. D. Pugliese, and J. M. Bobbitt, *J. Electrochem. Soc.*, **116**, 219 (1969).

(29) K. H. Weisgraber, Ph. D. Thesis, University of Connecticut, 1969.

(30) The melting points are corrected. Spectra were determined as follows: ir on Perkin-Elmer instruments (Models 137B and 21); nmr spectra on a Varian A-60 instrument against a tetramethylsilane standard; mass spectra on an AEI Model AS-12 instrument at 70 eV. Chromatography was carried out on thin (0.25-mm) and thick (1-mm) layers of silica gel GF_{254} and PF_{254} and on aluminum oxide GF_{254} (Brinkmann Instruments Westbury, N. Y.). Dragendorff's reagent-1, (J. M. Bobbitt, "Thin-Layer Chromatography," Reinhold Publishing Co., New York, N. Y., 1963, p 93), aqueous 1% $FeCl_3$, and methanolic 2,4-DNPH solution (A. I. Vogel, "Practical Organic Chemistry including Qualitative Organic Analysis," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 1051) were used as spray reagents. All of the reactions were monitored by tlc. Column chromatography was carried out on silica gel M (Hermann Brothers, Cologne, Germany) and on aluminum oxide, Woelm (Alupharm Chemicals, New Orleans).

was heated at reflux until the acid dissolved and for 0.5 hr more. The solution was evaporated to dryness under vacuum and the residue was taken up in 200 ml of dry xylene.[31] The solution of 10 was added over 30 min to a suspension of sodium ethyl acetoacetate, prepared from 1.54 g (0.067 mol) of sodium sand in 200 ml of xylene and 8.7 g (0.067 mol) of ethyl acetoacetate. The resulting orange-yellow mixture was stirred at room temperature for 16 hr, filtered to remove a fine white precipitate of NaCl, and evaporated, under vacuum, to a brown oil. The oil crystallized when cooled over ice and recrystallized from absolute ethanol to give 21.3 g (81%) of yellow needles, mp 110.5–111.5°.

Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 70.04; H, 6.14.

Ethyl 3-Keto-5-(3-benzyloxy-4-methoxyphenyl)-4-pentenoate (12).—Anhydrous ammonia was allowed to bubble through an ice-cold solution of 19.65 g (0.046 mol) of 12 in 500 ml of dry xylene for 1 hr. The turbid mixture was allowed to come to room temperature and was stirred for 16 hr. The mixture was filtered and evaporated, under vacuum, to a brown, viscous oil which crystallized when placed in the cold. Recrystallization from 250 ml of absolute ethanol gave 14.6 g (83%) of light yellow 12, mp 84–88.5°. Compound 12 was used for the next step without further purification.

1-Carbethoxy-2-keto-4-(3-benzyloxy-4-methoxyphenyl)(e)-*trans*-quinolizidine (13).—α-Tripiperideine (7) was prepared by the method of Schöpf and coworkers[14] and was seeded with an authentic sample.[15] The acryloylacetic ester 12 (1.5 g, 0.0042 mol) and α-tripiperideine (0.35 g, 0.0043 mol) were stirred in 200 ml of 95% ethanol for 48 hr. Tlc (silica gel GF, benzene–ethyl acetate 5:1) showed the reaction to be complete in about 24 hr. Column chromatography gave 1.56 g of 13 (84% yield). In later experiments the product was crystallized directly from the reaction medium. Crystallization from absolute ethanol yielded the analytical sample: mp 116–116.5°; ir (KBr) μ 3.543 (Bohlmann band), 5.73, 5.762 (C=O); nmr ($CDCl_3$) τ 2.90 (m, 8, aromatic), 4.89 (s, 2, $OCH_2C_6H_5$), 5.78 (q, 2, OCH_2CH_3), 6.18 (s, 3, OCH_3), 6.68 (m, 2), 7.38 (m, 4), 8.47 (m, 10, OCH_2CH_3 and quinolizidine protons); ir ($CHCl_3$) μ 3.55, 3.70, (Bohlmann bands); mass spectrum *m/e* (relative intensity) 437 (8), 364 (12), 300, (13), 240 (19), 110 (15), 91 (100), 84 (48), 82 (27). The compound decomposed slightly when placed on a thin layer of silica gel G and warmed.

Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.09; H, 7.19; N, 3.25.

2-Keto-4-(3-benzyloxy-4-methoxyphenyl)(e)-*trans*-quinolizidine (14).—The quinolizidine ester, 13, (8.75 g, 0.02 mol) was suspended in 310 ml of 0.5% KOH in aqueous ethanol (1:1) and stirred at reflux for 17 hr. The hot solution was adjusted to pH 2–4 with 5% H_2SO_4 and the solution was allowed to cool for 20 min. A large excess of NH_4OH was added, and the mixture was extracted with $CHCl_3$ (three 100-ml portions). The $CHCl_3$ extracts were combined, dried (Na_2SO_4), filtered, and evaporated to a residue under vacuum. The resulting brown oil was taken up in hot methanol (50 ml). After 24 hr 1.5 g of 14 had crystallized. When the mother liquor was chromatographed on silica gel using benzene–ethylacetate (5:1) as developer, an additional amount (2.34 g, total yield 53%) of 14 was obtained. Crystallization from methanol gave the analytical sample, mp 169–170°: ir (KBr) μ 3.495, 3.566 (Bohlmann bands), 5.764 (C=O); nmr ($CDCl_3$) τ 2.90 (m, 8, aromatic), 4.90 (s, 2, $OCH_2C_6H_5$), 6.19 (s, 3, OCH_3), 6.59 (m, 3), 7.67 (s, 4), 8.50 (m, 7, quinolizidine); mass spectrum *m/e* (relative intensity) 365 (26), 274 (24), 250 (14), 191 (32), 110 (18), 91 (100), 84 (43), 82 (32).

Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.41; H, 7.39; N, 3.79.

Epimeric 2-Hydroxy-4-(3-benzyloxy-4-methoxyphenyl)(e)-*trans*-quinolizidines (15 and 16).—The tetraphenylborate salt of 14 was prepared by adding 1.132 g (0.0033 mol) of sodium tetraphenylboron in 100 ml of H_2O to a solution of 1.093 g (0.003 mol) of 14 in 100 ml of H_2O adjusted to pH 2 with concentrated HCl. The precipitated salt was collected and washed with H_2O to remove excess HCl.

The salt was dissolved in 100 ml of absolute methanol and cooled to ice temperature. Sodium borohydride (0.266 g, 0.006 mol) in 25 ml of cold methanol was added over 5 min to the stirred solution. After 20 min, a second portion (0.226 g) of sodium borohydride was added and the reaction was stirred for an additional 0.5 hr more. Tlc (silica gel GF, benzene–methanol 10:1 and 5:1) monitoring of the reaction showed the necessity of adding the second portion of borohydride, and also that the reaction was finally about 80% complete. The reaction mixture was then passed (500 ml in 16 hr) through a column (1.5 × 20 cm) of Dowex 1-X8-OH (previously washed with and suspended in ethanol). The column was washed with ethanol until no more Dragendorff-positive material was eluted. The ethanol was evaporated under vacuum to a dark oil which was chromatographed over 120 g of silica gel (previously dried at 110°) using benzene–methanol (10:1) as developer. Fractions of 15 ml were collected at a flow rate of 0.5 ml/min. Fractions 6–28 yielded 0.266 g of starting material 14. Fractions 32–63 contained 0.488 g of the equatorial epimer 15. Fractions 64–76 contained 0.050 g of a mixture of 15 and 16, and 77–132 contained 0.323 g of the axial epimer 16. The overall recovery from the column was 103%, and the yields of pure 15 and 16 were 59 and 39%, respectively, after correcting for recovered starting material.

The axial isomer 16 showed the following spectroscopic properties: ir (KBr and $CHCl_3$) μ 2.78, 2.98 (OH), 3.504, 3.559 (Bohlmann bands); nmr ($CDCl_3$) τ 2.78 (m, 8, aromatic), 4.83 (s, 2, $OCH_2C_6H_5$), 6.19 (s, 3, OCH_3), 5.88 (s, 1, carbinol proton), 7.23 (m, 2), 8.39 (m, quinolizidine); mass spectrum *m/e* (relative intensity) 367 (36), 276 (37), 154 (38), 110 (22), 91 (100), 84 (27), 82 (20). The compound crystallized from chloroform–ether to yield an analytical sample, mp 126–127°.

Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.44; H, 7.93; N, 3.87.

The equatorial alcohol 15 did not crystallize but showed spectral properties virtually identical with those of 16 except for the nmr peak of the carbinol proton which appeared at τ 6.49.

Methyl *p*-Benzyloxyhydrocinnamate (21).—Dry *p*-benzyloxyhydrocinnamic acid [mp 123–125° (lit.[26] mp 123–124°), 10 g, 0.039 mol] was heated at reflux with 9.2 g (0.078 mol) of $SOCl_2$ in 150 ml of dry benzene for 16 hr. The benzene was removed under vacuum, and the resulting syrup was dissolved in 200 ml of petroleum ether (bp 65–110°). This solution was combined and stirred with 50 ml of dry methanol. From this two phase system, the product began to crystallize after 15 min. After 7 hr, the solution was cooled, and the product (8.85 g, 84%) was collected and washed with cold petroleum ether. The compound showed the predicted spectral properties and melted at 81–82°.[32]

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.21; H, 6.66.

Epimeric 2-(*p*-Benzyloxyhydrocinnamoyloxy)-4-(3-benzyloxy-4-methoxyphenyl)(e)-*trans*-quinolizidines (17 and 18).—The two compounds were made in the following way. The alcohols 15 or 16 (0.642 g, 1.75 mmol) and 0.472 g (1.75 mmol) of 21 were dissolved in 125 ml of xylene and heated at reflux under a Dean-Stark separator for 1 hr. NaOMe (0.095 g, 1.75 mmol) suspended in xylene was added to the mixture and heating was continued for 21 hr. The reaction was monitored by tlc (silica gel GF, benzene–ethyl acetate 3:1). The reaction mixture was cooled and extracted three times with H_2O. The xylene was removed under vacuum and the brown residue was purified by column chromatography (40 g of silica gel in a 1.5 × 36 cm column, developed at 0.5 ml/min with benzene–ethyl acetate 5:1). Evaporation of the appropriate fractions yielded 0.750 g (70%) of 17 or 0.762 g (72%) of 18.

Crystallization of the axial epimer 18 from acetone–methanol yielded an analytical sample: mp 109–110°; ir (KBr) μ 3.50, 3.578 (Bohlmann bands), 5.748 (C=O); nmr (CCl_4) τ 2.97 (m, 17, aromatic), 5.09 (d, 4, $OCH_2C_6H_5$), 6.31 (s, 3, OCH_3), 7.28 (m, 5), 8.64 (m, 11, quinolizidine); mass spectrum *m/e* (relative intensity) 605 (9), 604 (18), 514 (10), 513 (26), 350 (17), 349 (14), 348 (25), 267 (3), 258 (15), 136 (32), 91 (100), 84 (16), 82 (10).

Anal. Calcd for $C_{39}H_{43}NO_5$: C, 77.33; H, 7.15; N, 2.31. Found: C, 77.06; H, 7.29; N, 2.30.

The equatorial epimer 17 did not crystallize, but the spectral properties were qualitatively the same as those of 18.

Anal. Found: C, 76.96; H, 7.22; N, 2.17.

(31) The acid chloride, 10, was isolated, and melted at 100–113°. However, because it was extremely sensitive to moisture, it was not further characterized.

(32) This compound was previously prepared [I. T. Strukov, *Zh. Obshch. Khim.*, **29**, 2914 (1959); *Chem. Abstr.*, **54**, 12110 (1959)] but was not crystallized.

Epimeric 2-(*p*-Hydroxylhydrocinnamoyloxy)-4-(3-hydroxy-4-methoxyphenyl)(e)-*trans*-quinolizidines (19 and 20).—The appropriate benzyl ether (17 or 18, 0.3 g) in absolute ethanol were hydrogenated over 0.06 g of 5% Pd–C. The theoretical amount of hydrogen was taken up in 4 hr. Removal of the catalyst and the solvent gave the two phenols, 19 or 20 in essentially quantitative yields. Neither crystallized and both were characterized as glasses.

The axial epimer 20 showed a softening point of 70–85° and had the following spectral properties: ir (KBr) μ 3.00 (OH), 3.59, 3.64 (Bohlmann bands), 5.82 (C=O); nmr ($CDCl_3$) τ 3.33 (m, 7, aromatic), 5.0 (s, phenolic), 6.24 (s, 3, OCH_3), 7.20 (m, 7), 8.59 (m, quinolizidine); mass spectrum *m/e* (relative intensity) 426 (28), 425 (100), 424 (17), 260 (70), 259 (50), 258 (67), 177 (72), 150 (20), 137 (22), 136 (65), 117 (33), 110 (15), 107 (63), 84 (71), 55 (22); uv (ethanol) the spectrum was shifted to a higher wave length upon NaOH addition.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.03; H, 7.32; N, 2.91.

The equatorial isomer 19 had spectral properties qualitatively similar to those of 20. It liquified at 65–75°.

Anal. Found: C, 69.91; H, 7.35; N, 2.89.

Registry No.—**9**, 24807-37-2; **11**, 24807-38-3; **12**, 24807-39-4; **13**, 24806-75-5; **14**, 24806-76-6; **15**, 24806-77-7; **16**, 24806-78-8; **17**, 24806-79-9; **18**, 24806-80-2; **19**, 24806-81-3; **20**, 24806-82-4; **21**, 24807-40-7.

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Chemistry of *Ottonia vahlii* Kth. II.[1] Constitution of the Nonvolatile Component[2]

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The nonvolatile principle (piperovatine) of the leaves, roots, and stems of *Ottonia vahlii* Kth., has been shown, by spectral study and synthesis, to be N-isobutyl-6-*p*-methoxyphenylsorbamide (1).

In an earlier communication[1] we identified the volatile constituent of the shrub *Ottonia vahlii* [syn. *Piper ovatum* (Vahl)], native to the West Indies, as 1-butyl-3,4-methylenedioxybenzene. In this paper we are concerned with the chemical structure of the nonvolatile component of the same plant.

The sole chemical studies of this shrub were published over 70 years ago.[5] The isolation from the leaves of a crystalline "alkaloid," mp 123°, was described; it was named piperovatine, assigned a molecular formula $C_{16}H_{21}NO_2$, and found to be neutral in reaction and to have marked physiological properties. It proved to be a temporary nerve depressant, a heart poison, a local anesthetic, and a powerful sialagogue when applied to the tongue.

We have isolated from the leaves, roots, and stems of this plant what appears to be the same compound by a simplified mode of extraction. Some difficulty was experienced with its purification, owing to the fact that, as noted by the earlier workers, crystallization attempts were attended by a strong tendency towards gel formation in a variety of solvents. Eventually a combination of high-vacuum sublimation followed by crystallization from a critical volume of ether yielded a crystalline product of maximum mp 121°. A sample of the earlier workers' product was not available for comparison, but there seems little doubt, from the physical and physiological properties of our material, that it is identical with piperovatine.

Elemental analysis and molecular-weight determination by mass spectrometry necessitated an alteration of the molecular formula to $C_{17}H_{23}NO_2$, containing one methoxyl group. The presence of the latter was confirmed, and its aromatic character was revealed by nmr spectroscopy (singlet, 3.82 ppm, 3 H). The neutral character of the product suggested it might be amidic. This was confirmed by its ir spectrum (in CCl_4): maxima at 3460 (free NH), 3380 (H-bonded NH), and 1673 cm^{-1} suggested the carbonyl group is conjugated with two double bonds. Bands at 1461 and 1438, and 1178 and 1171 are assigned to a $>C(CH_3)_2$ group, at 1243 to an aromatic OCH_3 group, and at 991 cm^{-1} to a *trans*,-*trans* CH=CH—CH=CH system conjugated with the amide carbonyl group.[6] The uv spectrum (λ_{max}^{EtOH} 262 mμ, ϵ 26,500) confirms the presence of a diene system conjugated with the amidic carbonyl group and further supports the belief that the double bonds are both *trans* in geometry [compare sorbic acid, λ_{max}^{EtOH} 263 mμ, ϵ 25,800).[7] The nmr spectrum revealed the following features in the molecule: (a) a *para*-disubstituted benzene ring (A_2B_2 pattern, centered at 6.90, 4 H); (b) olefinic protons (4 H) attached to a conjugated diene system [multiplicity of signals in the range 5.6–6.4; of these a doublet centered at 5.87 (J = 15 Hz) is assigned to an α proton *trans* to the β proton on the α,β C=C bond (compare sorbic acid[8])]; (c) an aromatic methoxyl group singlet at 3.82, 3 H); (d) a benzylic CH_2 group (doublet, J = 5 Hz, centered at 3.45, 2 H); (e) an apparent triplet centered at 3.20, J = 5 Hz (2 H), assigned to a $-NHCH_2CH<$ grouping, is in reality a quartet in which the two innermost signals overlap ($J_{CH-NH} = J_{CH-CH}$). On deuteration these signals collapse to a doublet centered at 3.12 (J = 7 Hz) [several model compounds containing the grouping $R\cdot C(O)\cdot NH\cdot CH_2CH<\begin{matrix}R'\\R''\end{matrix}$, were synthesized;

(1) Part I: A. R. Pinder and S. J. Price, *J. Chem. Soc. C*, 2597 (1967).

(2) Presented at the Annual Meeting of the South Carolina Academy of Science, Columbia, S. C., April 1968; at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968, and at The Third National Products Symposium, Kingston, Jamaica, W. I., Jan 1970.

(3) Submitted by S. J. Price in partial fulfillment of the requirements for the Degree of M.S., Clemson University, May 1969.

(4) To whom inquiries should be addressed.

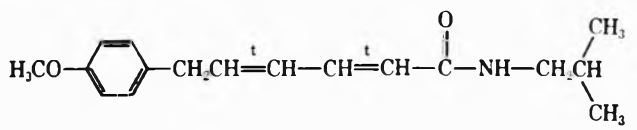
(5) W. R. Dunstan and H. Garnett, *J. Chem. Soc.*, **67**, 94 (1895). See also T. A. Henry, "The Plant Alkaloids," 4th ed, Churchill, London, 1949 p 2.

(6) For examples, see J. L. H. Allan, G. D. Meakins, and M. C. Whiting, *J. Chem. Soc.*, 1874 (1955).

(7) (a) U. Eisner, J. A. Elvidge, and R. P. Linstead, *ibid.*, 1372 (1953); (b) see also A. I. Scott, "Interpretation of the UV Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964, p 81.

(8) Varian Associates NMR Spectral Catalog, Vol. 2, spectrum no. 462.

all had the N–CH_2 signal as an apparent triplet]; (f) a methine hydrogen in a grouping $CH_2CH(CH_3)_2$ (multiplet, 1 H, 1.1–2.2); and (g) an isopropyl group, the methyl hydrogens of which appeared as a doublet, J = 7.5 Hz (6 H), centered at 0.95 ppm.



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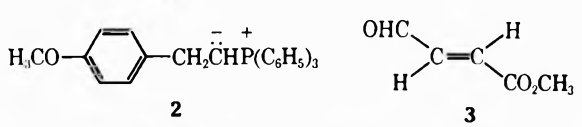
The information so far accumulated points to structure 1 for piperovatine. This formulation is supported by its mass spectrum, which has a parent ion peak at m/e 273. Fragmentation peaks at m/e 201, 173, 152, 121, and 100 are assigned to ions $[H_3COC_6H_4CH_2(CH{=}CH)_2CO]^+$, $[H_3COC_6H_4CH_2(CH{=}CH)_2]^+$, $[(CH{=}CH)_2CONHCH_2CH(CH_3)_2]^+$, $[H_3CO{-}C_6H_4{-}CH_2]^+$, and $[OCNHCH_2CH(CH_3)_2]^+$, respectively. A peak at 217 may be due to a McLafferty rearrangement to $[H_3COC_6H_4CH_2(CH{=}CH)_2CONH_2]^+$, with elimination of isobutene.[9]

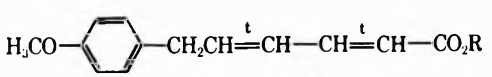
Support is also provided by the facts that piperovatine on acid hydrolysis generates isobutylamine, and on quantitative catalytic hydrogenation takes up 2 mol of hydrogen.

The proposed structure was confirmed by the following synthesis. Reduction of ethyl *p*-methoxyphenylacetate with lithium aluminum hydride afforded *p*-methoxyphenethyl alcohol, converted by phosphorus pentabromide into the corresponding bromide.[10] Reaction of the latter with triphenylphosphine generated the expected *p*-methoxyphenethyltriphenylphosphonium bromide as a syrup which solidified on cooling. Attempts to purify this salt were unsuccessful; the solid mass was pulverized and converted into its ylide **2** by treatment with *n*-butyllithium. The ylide was treated with methyl *trans*-3-formylacrylate (**3**), obtained by selenium dioxide oxidation of methyl crotonate.[11] The product proved to be mainly the desired dienoic ester **4a**, contaminated with a geometrical isomer thereof, as indicated by its uv absorption (relatively wide λ_{max}^{EtOH} 260–265 mμ, with low ε 15,000–

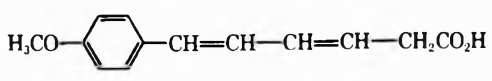


2

3



4a, R = CH_3
b, R = H



5

17,000),[7b] and by tlc analysis, which showed the presence of two major components, with similar R_f values. Recent studies on the stereochemical outcome of Wittig reactions[12] have shown that ylides enjoying resonance stabilization yield in the main *trans* alkenes, whilst ylides not so stabilized afford mixtures composed largely of *cis* alkenes. Ylide **2** is not resonance stabilized, and consequently it might have been anticipated that a mixture of isomers would result.

Treatment of a hexane solution of the product with a trace of iodine in sunlight[13] yielded a homogeneous all-*trans* ester **4a** (single spot on tlc), which crystallized easily. The all-*trans* configuration is assigned to it on spectral evidence: λ_{max}^{EtOH} 264 mμ (ε 25,500) and $\nu_{max}^{CCl_4}$ 1704, 1631, 1605, 994 cm^{-1}, both consistent with the presence of a CH=CH—CH=CH—CO grouping. The nmr spectrum showed a doublet (1 H, J = 15 Hz) centered at δ 5.87, which may be assigned to a proton α to the carbonyl group and *trans* to the β proton. The other features of the nmr spectrum were consonant with structure **4a**.

Hydrolysis of ester **4a** to the corresponding acid **4b** was first attempted with alkali, but it became clear on uv absorption measurement (λ_{max}^{EtOH} *ca.* 280–285 mμ, wide maximum) that the product was severely contaminated with the acid **5**, in which the double bonds have shifted into conjugation with the aromatic nucleus. This behavior was not unexpected, since analogous base-catalyzed isomerizations of compounds of the type $ArCH_2(CH{=}CH)_2CO_2CH_3$ (Ar = 2-thienyl, phenyl) have been described by Winterfeldt.[14] Fortunately, acid hydrolysis of **4a** furnished the corresponding acid, without isomerization (λ_{max}^{EtOH} 262 mμ). This acid did not react cleanly with thionyl chloride, but was smoothly converted by oxalyl chloride into its chloride.[13] The latter was not isolated but was condensed directly with isobutylamine to yield N-isobutyl-6-*p*-methoxyphenylsorbamide (**1**), which after high-vacuum sublimation and crystallization from ether had mp 121°, alone or mixed with an authentic sample of piperovatine, with which it was found to be identical in all respects. It will be evident that piperovatine must be reclassified as one of the increasing number of amides of vegetable origin.[15]

Experimental Section

Nmr measurements were made on a Varian A-60 instrument, with the assistance on occasion of a Varian C-1024 time-averaging computer, and using tetramethylsilane (TMS = 0) as internal reference. Thin layer chromatography (tlc) was effected on Merck silica gel plates (0.25 mm), with detection by iodine.

Isolation of Piperovatine.—Roots, leaves, and stems of dried *P. ovalum* plants were ground up finely, 600–650 g of this material being packed loosely into a linen bag and extracted with petroleum ether (bp 60–90°, 1500 ml) in a modified Soxhlet apparatus for 48 hr. The extract was concentrated to about 250 ml, filtered hot, and set aside at ambient temperature. The crystalline deposit was collected, washed with petroleum, and dried *in vacuo* (2.1 g). Attempts to recrystallize this product from a variety of solvents were unsuccessful, owing to gel formation.

(9) F. W. McLafferty, *Appl. Spectrosc.*, **11**, 148 (1957); *Anal. Chem.*, **31**, 82 (1959).
(10) J. B. Shoesmith and R. J. Connor, *J. Chem. Soc.*, 2230 (1927).
(11) F. Bohlmann and E. Inhoffen, *Chem. Ber.*, **89**, 1276 (1956).
(12) See, *inter al.*, L. D. Bergelson and M. M. Shemyakin, *Tetrahedron*, **19**, 149 (1963); L. D. Bergelson, L. I. Barsukov, and M. M. Shemyakin, *ibid.*, **23**, 2709 (1967); M. Schlosser and K. F. Christmann, *Justus Liebigs Ann. Chem.*, **708**, 1 (1967); W. P. Schneider, *Chem. Commun.*, 785 (1969).
(13) Compare P. E. Sonnet, *J. Org. Chem.*, **34**, 1147 (1969).
(14) E. Winterfeldt, *Chem. Ber.*, **96**, 3349 (1963).
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It was purified by high-vacuum sublimation (0.05 mm), from an oil bath at 105–110°, to yield 60 mg of a white, microcrystalline product, mp 110–115°. A resublimation did not raise the melting point. Tlc of the twice-sublimed material, with development by ether–benzene (9:1), showed one major spot and a minor one of slightly lower R_f value. A careful crystallization of this product was effected by dissolving it in a fairly large volume of dry ether, then concentrating until, on slow cooling, crystallization rather than gel formation occurred. The matted needles (30 mg) so obtained had mp 120–121° (lit.[5] mp 123°) and showed a single spot on tlc. Spectral properties: λ_{max}^{EtOH} 262 mμ (ε 26,500); $\nu_{max}^{CCl_4}$ 3460, 3380, 3024, 2830, 1673, 1636, 1610, 1461, 1438, 1243, 1178, 1171, 1038, 991, and 939 cm^{-1}; nmr 0.95 (d, J = 7.5 Hz, 6 H), 1.10–2.20 (m, br, 1 H), 3.20 (t, J = 5 Hz, 2 H), 3.45 (d, J = 5 Hz, 2 H), 3.82 (s, 3 H), 5.6–6.3 (4 H), and 6.90 ppm (A_2B_2 pattern, 4 H).

The mass spectrum showed peaks at m/e 273 (parent ion), 217, 201, 174, 173, 158, 152, 139, 135, 128, 121, 115, 110, 101, 100, 96, 91, 83, 78, and 65.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.73; H, 8.42; N, 5.13; OCH_3, 11.34; mol wt, 273.4. Found: C, 74.41; H, 8.18; N, 4.99; OCH_3, 11.01; mol wt (mass spectrum), 273.

Later work showed that the product was more abundant in the roots or stems than in the leaves. In agreement with Dunstan and Garnett[5] the compound produces local anesthesia and a sharp burning sensation when rubbed on the tongue. It is insoluble in water, dilute aqueous alkali, and dilute acid, sparingly soluble in hydrocarbon solvents and ether, and readily soluble in methylene chloride, chloroform, and carbon tetrachloride.

Hydrolysis of Piperovatine.—Piperovatine (150 mg) and 4 N hydrochloric acid (25 ml) were boiled under reflux for 6 hr. The cooled, clear solution was rendered strongly alkaline with solid potassium hydroxide and then extracted continuously with ether for 48 hr. The ether solution was dried (KOH) and the solvent evaporated *via* a long Vigreux column to small bulk. The final solution was mixed with an excess of an ether solution of picric acid and the yellow precipitate which separated was collected, dried, and crystallized from ethanol, from which it separated in yellow prisms, mp 150–151°, alone or mixed with an authentic sample[16] of isobutylamine picrate, mp 150°.

Hydrogenation of Piperovatine.—Adams platinum oxide catalyst (25 mg) was prereduced in ethanol in a microhydrogenation apparatus. When no further hydrogen was absorbed, piperovatine (13.2 mg) was added and agitation resumed. Absorption of hydrogen was complete in 30 min and measured 2.40 ml at 740.9 mm and 24.3° (2.42 ml = $2H_2$).

***p*-Methoxyphenethyltriphenylphosphonium Bromide.**—Ethyl *p*-methoxyphenylacetate (61.4 g) in dry ether (100 ml) was added gradually, dropwise, to a stirred and cooled suspension of lithium aluminum hydride (6.5 g) in dry ether (150 ml) during 2 hr. After a further 2 hr of stirring Celite (2 g) was added, followed by the gradual addition of ice water until decomposition was complete. The ether was decanted and the inorganic residue was leached repeatedly with ether. The combined ether extracts were dried (Na_2SO_4) and the solvent was removed. The residual 2-*p*-methoxyphenylethanol distilled at 96–97° (0.15 mm) [lit.[17] bp 102–105° (0.3 mm)]: 32.2 g, 67%; ν_{max}^{film} 3230 cm^{-1}, no carbonyl band.

Phosphorus pentabromide (52.4 g) was suspended in dry benzene (150 ml) and stirred at 0° during the gradual (30 min) addition of the above alcohol (18.5 g) in dry benzene (50 ml). Dry air was drawn through the solution for 4 hr, and then it was washed with water, dried (Na_2SO_4), and concentrated. The residual *p*-methoxyphenethyl bromide distilled at 98–101° (0.2 mm) [lit.[10] bp 130–131° (11 mm)]: 15.2 g, 58%.

Triphenylphosphine (6.6 g) was dissolved in dry xylene (50 ml) along with the foregoing bromide (5.3 g), and the whole mixture refluxed in a bath at 170° for 6 hr. On cooling, an oily layer separated and quickly solidified. The xylene was decanted and the residue was rapidly ground to a fine powder and freed from solvent by keeping several hours *in vacuo*. The phosphonium bromide (8.8 g, 75%) had mp 80°, with sintering at 68°. It appeared to be amorphous, and attempts to purify it by crystallization from a variety of solvents failed, in part owing to its highly hygroscopic nature. It was stored *in vacuo* over phosphorus pentoxide.

Methyl *trans,trans*-6-*p*-Methoxyphenylhexa-2,4-dienoate (4a).—Methyl crotonate was oxidized with selenium dioxide in dioxane solution, as described by Bohlmann and Inhoffen.[11] The methyl *trans*-3-formylacrylate (3) so obtained distilled at 90–97° (25 mm) and crystallized easily on cooling. A suspension of *p*-methoxyphenethyltriphenylphosphonium bromide (12.9 g, 0.027 mol) in dry ether (400 ml) was stirred under nitrogen at room temperature during the gradual (5 min) addition of a 1.6 N hexane solution of *n*-butyllithium (20 ml). The resulting deep orange ylide solution was stirred for 1.5 hr, and then transferred under nitrogen to a pressure-equalized dropping funnel and added during 20 min, under nitrogen, to a stirred solution of methyl *trans*-3-formylacrylate (2.5 g, 0.025 mol) in dry ether (100 ml). The lighter-colored solution was stirred overnight at ambient temperature, and then freed from most of the triphenylphosphine oxide and lithium bromide by filtration. The filtrate was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and water, and dried and concentrated, finally *in vacuo*, yielding the crude dienoic ester (1.6 g, 28%) as a mixture of geometrical isomers. The product was dissolved in petroleum ether (bp 30–60°) and chromatographed on alumina (15 g) with elution with the same solvent, yielding a purified product (1.0 g) which showed two major spots on tlc, with R_f values of the same order, using petroleum ether (bp 30–60°)–ethyl acetate (4:1) for development. A solution of this product in hexane (250 ml) was kept under nitrogen, treated with a crystal of iodine, and exposed to direct sunlight for 10 min. The solution was washed with sodium thiosulfate solution and water, dried, and the solvent was removed. The residue (1.0 g) solidified readily and showed only one spot on tlc (conditions as above). Methyl *trans,trans*-6-*p*-methoxyphenylhexa-2,4-dienoate separated from hexane in prisms: mp 78–80°; bp 160° (bath) (0.07 mm); λ_{max}^{EtOH} 264 mμ (ε 25 500); $\nu_{max}^{CCl_4}$ 1704 (conjugated C=O), 1631, 1605 (two conjugated C=C), 1238 (aromatic ether), and 994 cm^{-1} (*trans,trans* CH=CH—CH=CH); nmr 3.50 (d, J = 6 Hz, 2 H, benzylic CH_2), 3.80, 3.85 (two s, each 3 H, aromatic and ester OCH_3), 5.70–6.35 (m, 4 H, olefinic H), and 7.05 ppm (A_2B_2 pattern, 4 H, aromatic H).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.68; H, 7.13.

***trans,trans*-6-*p*-Methoxyphenylhexa-2,4-dienoic Acid (6-*p*-Methoxyphenylsorbic Acid) (4b).**—The foregoing methyl ester (0.5 g), freshly distilled dioxane (25 ml), concentrated hydrochloric acid (7.5 ml), and water (5 ml) were heated under reflux on the steam bath for 16 hr. To the cooled mixture was added excess solid sodium bicarbonate. Neutral matter was removed by ether extraction, and the aqueous layer was acidified with 5 N hydrochloric acid. The semisolid material which separated was taken up in ether, and the solution was washed with water, dried, and concentrated. The oily residue (0.4 g) solidified readily; it was purified by vacuum distillation, bp 160–165° (bath) (0.04 mm), followed by crystallization from petroleum ether (bp 60–90°), from which it separated in clusters of feathery needles (0.4 g), mp 115°, λ_{max}^{EtOH} 262 mμ (ε 20,400).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; equiv, 218.2. Found: C, 71.67; H, 6.51; equiv, 218.5.

N-Isobutyl-6-*p*-methoxyphenylsorbamide (1).—The above acid (0.5 g) in dry ether (50 ml) was treated with oxalyl chloride (10 ml) and the mixture was kept at room temperature overnight with rigid exclusion of moisture. The solvent and excess oxalyl chloride were removed *in vacuo* and the residue was dissolved in dry ether (100 ml) and cooled in ice. A solution of isobutylamine (1.5 g) in dry ether (100 ml) was added gradually with agitation. After completion of the addition, the ethereal suspension was washed with dilute hydrochloric acid, water, and aqueous sodium bicarbonate, and then dried and concentrated. The solid residue (0.55 g) was purified by sublimation [105–110° (bath) (0.05 mm)] followed by crystallization from a critical volume of dry ether, from which it separated in matted needles or small prisms (0.35 g), mp 121°, alone or mixed with an authentic specimen of piperovatine. The spectral and tlc properties of the natural and synthetic materials were identical.

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Registry No.—**1**, 25090-18-0; **4a**, 25090-19-1; **4b**, 25090-20-4.

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Side-Chain Transformations and Deuterium Labeling in the Steroidal Sapogenin Series[1]

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Synthetic transformations, notably through introduction of double bonds into rings E and F, have led to the preparation and characterization of a significant number of new derivatives of the basic nucleus of the steroidal sapogenin, (25*R*)-5α-spirostan, and to thirteen mono- or polydeuterated analogs. In the course of the work, it was possible to study the effect of acidic reagents on the spiroketal side chain, the ease of exchange proceeding in the order 23 >> 20 >>> 25. The availability of the various deuterium-labeled sapogenins proved of great value for many nmr assignments in this class of natural products.

In years past, synthetic work in the field of steroidal sapongenins has taken a number of directions. Characterization of unknown species either by direct chemical manipulation or by interconversion led Marker[4] and, more recently, others[5] to the identification of a wealth of these natural products. Degradation of the spiroketal side chain by modifications[6] of the original Marker procedure[7] afforded new and industrially important routes to such important hormones as the pregnanes,[7-9] cortisone,[8,9] and certain progestational agents.[8,9]

During the past 10 years, two groups[10,11] have reported total syntheses of members of this class; in addition, biosynthetic studies[12] and biodegradation experiments[13] have also appeared. Over the years the usual spectroscopic techniques, such as infrared,[14] ultraviolet,[15] nuclear magnetic resonance,[16] optical rotatory dispersion,[17] and mass spectrometry,[18] have been extensively applied with special reference to the spiroketal system of these sapogenins.

In this laboratory, in connection with a detailed study[18a] of the mass spectrometric behavior of steroidal sapogenins, it became necessary to introduce deuterium at numerous positions of the fundamental skeleton, namely (25*R*)-5α-spirostan or 3-deoxytigogenin (**1**).[19] We felt that such deuterium labeling, though laborious, would not only afford useful mass spectrometric information but would also aid in the interpretation of nuclear magnetic resonance spectra[16] by simplifying splitting patterns and by adding data to the Zürcher-type tables of Tori and Aono.[16e] With relatively few exceptions,[20] most of the chemical studies in this series have involved degradation of the spiroketal system rather than substitutions of the intact side chain. Consequently, our work was likely to contribute to this relatively scarcely studied aspect of sapogenin chemistry.

The problem which we faced may be stated as follows: starting with the basic sapogenin nucleus, **1**,

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(2) Taken, in most part, from the Ph.D. Thesis of W. H. F., National Institutes of Health Predoctoral Research Fellow, 1966–1970.

(3) Postdoctoral Research Fellow, 1965–1966.

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(19) The sapogenin nomenclature used in this paper follows the IUPAC-IUB 1969 Revised Tentative Rules for Steroid Nomenclature, *Steroids*, **13**, 278 (1969), or *J. Org. Chem.*, **34**, 1517 (1969). In cases where a trivial name has been used in the literature for many years, it will be used (along with the proper nomenclature, in some cases) upon its first mention in the article. However, because sapogenin nomenclature has changed a number of times throughout the years, only the proper name will be used thereafter.

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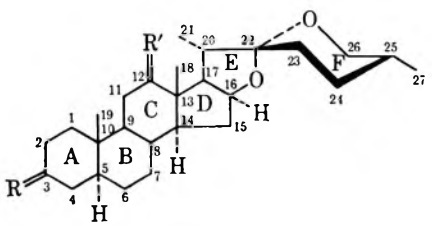
find methods to functionalize positions, especially those in rings E and F, so that the usual deuterating reagents,[21] *e.g.* D_2, D_2O, $LiAlD_4$, $NaBD_4$, CH_3OD, CH_3COOD, DCl, etc., can be used to incorporate deuterium in a specific manner.

(25*R*)-5α-Spirostan (**1**) was prepared in good yield from hecogenin acetate (**2**) by Huang-Minlon reduction to tigogenin (**3**), followed by Jones oxidation[22] to tigogenone (**4**) and repeated Huang-Minlon reduction.



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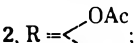
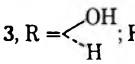
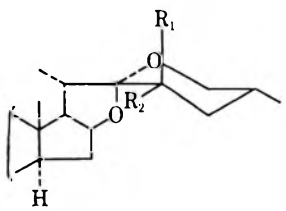
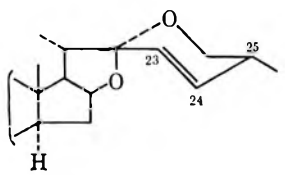
2, R =  ; R′ = O

3, R =  ; R′ = H_2

4, R = O; R′ = H_2

Our initial task was to introduce double bonds into the spiroketal system, a plan which apparently had not been attempted before. For this purpose, **1** was brominated by Callow's method[16a] to afford an easily separable mixture of 23,23-dibromo- (**5**), 23*R*-bromo- (**6**),[16f] and 23*S*-bromo-(25*R*)-5α-spirostan (**7**).[16f] In addition, a minor modification of the original bromination procedure[23] gave quantitative conversion to a mixture of the monobromides **6** and **7**.



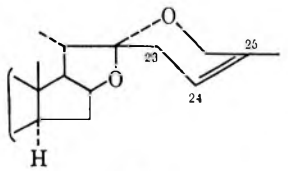


5, $R_1 = R_2 = Br$

6, $R_1 = Br$; $R_2 = H$

7, $R_1 = H$; $R_2 = Br$

8



9

In our hands, only the axial bromide **6** could be made to eliminate even under strong dehydrominating conditions[24] (potassium *t*-butoxide in DMSO–benzene). At room temperature, the reaction gave (25*R*)-5α-spirost-23-ene (**8**) while, at about 100°, the same procedure afforded the isomeric, trisubstituted olefin 5α-spirost-24-ene (**9**) through base abstraction of the tertiary, allylic proton at C-25 in the disubstituted olefin **8**.[25] The direct conversion of **8** to **9** was experimentally verified. In practice, the dehydrobromination was run on the monobromide mixture since the unreactive equatorial bromide **7** can be separated easily from the product olefin, **8** or **9**.

Since lithium aluminum deuteride reduction of tosylates is one of the most specific (position, stereochemistry, per cent incorporation) methods of deuterium introduction,[21] the isomeric olefins were converted to the respective epoxides, 23*R*,24*R*-epoxy-(25*S*)- (**10**), 23*S*,24*S*-epoxy-(25*S*)- (**11**), 24*S*,25*R*-epoxy- (**12**), and 24*R*,25*S*-epoxy-5α-spirostan (**13**), which were then opened to the alcohols **14**, **15**, and **17**–**19** (see Scheme I)[26,27] with lithium aluminum hydride.

The alcohol **17**, obtained from both epoxides **11** and **13**, is the key compound in defining the stereochemistry of essentially all of the others in Scheme I. Since it was derived from the trisubstituted epoxide **13**, it must be a 24-alcohol because the nmr spectrum exhibits a doublet for CH_3-27 in addition to the one for CH_3-21. In the infrared, the hydroxyl absorption, which did not shift upon dilution, appears at 3490 cm^{-1} indicating intramolecular hydrogen bonding, thus proving that the configuration must be *R* (as shown) since, with that stereochemistry, the ring E oxygen and the 24-hydroxyl are in a 1,3-diaxial relationship. All of the other alcohols exhibit hydroxyl absorptions in the range of 3560–3592 cm^{-1} indicating nonhydrogen bonded species. Thus, assuming no change of stereochemistry at the epoxide carbon–oxygen bond which is not opened by hydride, the stereochemistry of the epoxides **10**–**13** follows directly. Since alcohols **15** and **19** were obtained along with **17** from epoxides **11** and **13**, respectively, their configurations must be as indicated. That the alcohol **18** is the tertiary isomer of **19** and not the secondary alcohol **16** is proved by the nmr spectrum which exhibits three tertiary methyl singlets (CH_3–18,19, and 27). From models, one expects that a change of hydroxyl

(21) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," "Alkaloids," Vol I, Holden-Day, San Francisco, Calif., 1964, pp 17–40. See also (b) M. Fétizon and J. C. Gramain, *Bull. Soc. Chim. Fr.*, 651 (1969).

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

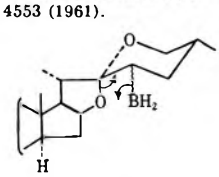
(23) C. Djerassi, H. Martinez, and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951). See also references 16a and 16f.

(24) (a) J. E. Hofmann, T. J. Wallace, and A. Schriesheim, *J. Amer. Chem. Soc.*, **86**, 1561 (1964); (b) T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *ibid.*, **85**, 2739 (1963).

(25) The isomerization of olefins under strongly basic conditions is well verified: (a) C. Cerceau, M. Laroche, A. Pazdzerski, and B. Blouri, *Bull. Soc. Chim. Fr.*, 921 (1969); (b) S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *J. Amer. Chem. Soc.*, **89**, 6897 (1967); (c) S. Bank, C. A. Rowe, Jr., and A. Schriesheim, *ibid.*, **85**, 2115 (1963); (d) A. Schriesheim, C. A. Rowe, Jr., and L. Naslund, *ibid.*, **85**, 2111 (1963); (e) A. Schriesheim, R. J. Muller, and C. A. Rowe, Jr., *ibid.*, **84**, 3164 (1962); (f) A. Schriesheim and C. A. Rowe, Jr., *ibid.*, **84**, 3160 (1962); (g) A. Schriesheim and C. A. Rowe Jr., *Tetrahedron Lett.*, 405 (1962); (h) A. Schriesheim, J. E. Hofman, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **83**, 3731 (1961).

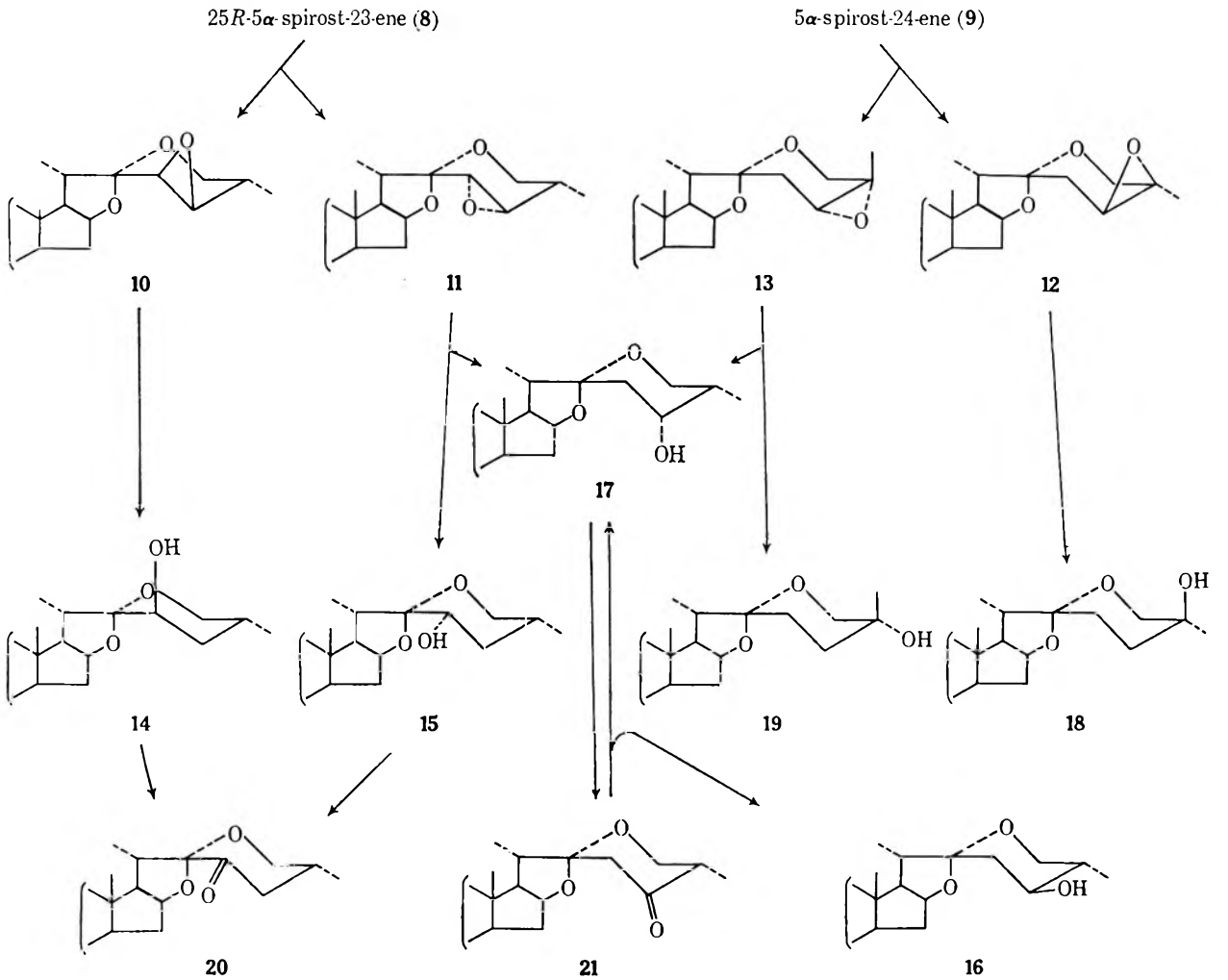
(26) Since the plane of ring F is perpendicular to the plane of the paper, the practice of designating the stereochemistry of substituents located on carbons 23–26 by dotted and solid lines and calling them "α" and "β," respectively, cannot properly be done (see reference 19). However, more clarity is obtained in Scheme I if, as one looks from the "top" of ring F, the substituents below the ring are designated by dotted lines and the ones above the ring by solid lines.

(27) One might suggest that the alcohols and even the deuterated compounds be prepared through hydroboration of the olefins [M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964)]. This procedure was, in fact, tried on the olefin **8** but gave at least twelve products owing, possibly, to an initial elimination of type i. See also G. R. Pettit and T. R. Kasturi, *ibid.*, **26**, 4553 (1961).



i

SCHEME I



configuration from 23*S* to 23*R* (**15** to **14**) would affect the nmr absorption of CH_3-21 much more than that of CH_3-27 since in **14**, the hydroxyl is situated essentially in a 1,3-diaxial relationship to CH_3-21, a situation known[28] to produce a strong downfield shift. The change 24*R* to 24*S* (**17** to **16**) would affect CH_3-27 more than CH_3-21. A 16-Hz downfield shift of CH_3-21 from **15** to **14** as well as oxidation of both to the same ketone **20** confirmed the structure of **14**. Lithium aluminum hydride reduction of the 24-ketone **21**, derived from alcohol **17**, unfortunately afforded **17** as the major product. However, the isomer **16** (24*S*) was obtained in small yield.

The nmr chemical shift data for all compounds **8** through **21** appear in Table I. We had hoped to determine the stereochemistry of both members of each epoxide pair by nmr, but results were inconclusive because, even though there are indications that ring F is in the form of a half-chair[29] and, though ample data are available for predicting chemical shifts[29a] and coupling constants,[30] the way to build a model from which to calculate is not clear owing to the possible inversion of ring F from one half-chair to another as in the case of cyclohexene,[31] a situation which greatly complicates matters. Regular steroid models[29a] do not show the same relative spacial orientations between epoxide and methyl group.

Unfortunately, tosylate formation[32] of the most readily available secondary alcohol, (25*S*)-5α-spirostan-24*R*-ol (**17**), proved abortive as did tosylhydrazone formation[33] and electrolytic reduction[34] of the derived ketone, (25*S*)-5α-spirostan-24-one (**21**).

Since ketals are known to be sensitive to acid, we considered next the possibility of acid-catalyzed exchange of the spiroketal system in a deuterium-containing medium. A number of workers[35-37] have explored this type reaction but have never applied nuclear magnetic resonance or mass spectrometry to the problem of the location and amount of incorporated deuterium. 1,4-Dioxaspiro[4.5]decane (A) shows an nmr absorption[38] for protons a at δ 1.51; so the "spike" at 1.59 in

(28) K. Tori and T. Komeno, *Tetrahedron*, **21**, 309 (1965). See especially p 318.

(29) (a) K. Tori, T. Komano, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964); (b) A. McL. Mathieson, *Tetrahedron Lett.*, 31 (1963).

(30) (a) Reference 29a, pp 1139–1141; (b) K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *ibid.*, 559 (1964).

(31) F. A. L. Anet and M. Z. Haq, *J. Amer. Chem. Soc.*, **87**, 3147 (1965).

(32) (a) Reference 5f, p 770; (b) P. S. Wharton and G. A. Hiegel, *J. Org. Chem.*, **30**, 3254 (1965) (sodium hydride method).

(33) M. Fischer, Z. Pelah, D. H. Williams, and C. Djerassi, *Chem. Ber.*, **98**, 3236 (1965).

(34) L. Throop and L. Tokés, *J. Amer. Chem. Soc.*, **89**, 4789 (1967).

(35) Reference 16a, especially pp 293 and 296.

(36) R. K. Callow and P. N. Massy-Beresford, *J. Chem. Soc.*, 2645 (1958).

(37) R. B. Woodward, F. Sondheimer, and Y. Mazur, *J. Amer. Chem. Soc.*, **80**, 6693 (1958).

(38) Sadtler Spectrum No. 430M published by Sadtler Research Laboratories, Inc., Philadelphia, Pa. 19104.

TABLE I

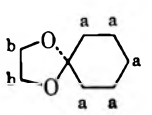
NUCLEAR MAGNETIC RESONANCE DATA OF SOME STEROIDAL SAPOGENINS[a]

Compd no.	Description[b]	δ, ppm, from TMS: 19 H	18 H	21 H	27 H	Other H[c]
1[f]		0.794	0.760	0.95€ (d, 6.6)	~0.776 (d, ~6)	23 H_2 1.59
5	23,23-dibromo-	0.800	0.994	1.22€ (d, 6.9)	0.833 (d, ~6.6)	
6[g]	23*R*-bromo-	0.797	0.797	1.17€ (d, 7.0)	0.803 (d, 6.2)	
7[g]	23*S*-bromo-	0.801	0.883	0.932 (d, 7.0)	0.815 (d, 6.0)	
8	Δ^{23}	0.803	0.803	0.922 (d, 6.8)	0.874 (d, 7.2)	5.83 (23 H, m, 10 and 2) 5.53 (24 H, m, 10)
9	Δ^{24}	0.791	0.781	1.003 (d, 6.7)	1.600 (s)	5.42 (24 H, m)
		0.87	0.77	1.16 (d, 6.5)	1.53 (s)	pyr (60-MHz nmr)
10	23*R*,24*R*-epoxy-(25*S*)-	0.799	0.833	0.951 (d, 7.3)	1.047 (d, 7.0)	2.92 (23 H, 24 H, m) 3.4 (26 H_2, m); 4.5 (16 H, m)
11	23*S*,24*S*-epoxy-(25*S*)-	0.803	0.850	0.992 (d, 6.8)	0.992 (d, ~6.5)	3.2 (23 H, 24 H, m) 3.3 (26 H_2, m); 4.5 (16 H, m)
12	24*S*,25*R*-epoxy-	0.796	0.761	0.960 (d, 6.5)	1.278 (s)	3.21 [24 H, m, d (?), ~5] 3.66 (26 H_a, d, 12); 3.83 (26 H_e, d, 13); 4.35 (16 H, m)
13	24*R*,25*S*-epoxy-	0.788	0.752	0.948 (d, 6.€)	1.365 (s)	3.11 (24 H, m) 3.75 (26 H_a, d, 12); 4.05 (26 H_e, d, 13) 4.3 (16 H, m)
14	23*R*-hydroxy-(25*R*)-	0.796	0.784	1.104 (d, 7.0)	0.798 (d, 6.0)	
15	23*S*-hydroxy-(25*R*)-	0.802	0.802	0.943 (d, 6.9)	0.813 (d, 6.0)	
16	24*S*-hydroxy-(25*S*)-	0.80	0.77	0.98 (d, 6.2)	0.93 (d, 6.6)	(approximate values)
17	24*R*-hydroxy-(25*S*)-	0.795	0.761	0.956 (d, 7.0)	0.870 (d, 6.9)	
18	25*S*-hydroxy-	0.790	0.768	1.018 (d, 6.2)	1.102 (s)	(60-MHz nmr) 2.4 (–OH)
19	25*R*-hydroxy-	0.790	0.758	0.967 (d, 6.2)	1.289 (s)	(60-MHz nmr) 2.1 (–OH)
20	23-oxo-(25*R*)-	0.792	0.769	0.927 (d, 6.9)	0.927 (d, 6.9)	4.60 (16 H, m); 2.85 (20 H, m); 2.42 [24 H, s (?)]; 3.7 (26 H_2, m)
21	24-oxo-(25*S*)-	0.795	0.756	0.958 (d, 6.6)	1.071 (d, 6.6)	4.3 (16 H, m); ~2.4 (23 H_a, d, 14); ~2.6 (23 H_e, d, 14); 25 H under 23; 3.6 (26 H_a, m, 11 and 11); 3.9 (26 H_e, m, 12 and 8)
24	20-deuterio-(25*R*)-	0.794	0.758	0.951 (s)	0.778 (d, 6.0)	
26	24*S*,25*R*-dideuterio-	0.790	0.758	0.952 (d, 6.6)	0.770 (s)	4.367 (16 H, m, 7.5, 6.75, and 7.6); 1.576 [23 H_2, s (?)]; 3.338 (26 H_a, d, 6.9); 3.448 (26 H_e, d, 6.6)
29	(20*S*,22ξ,25*R*)-5α-furostan-26-ol	0.792	0.792	0.980 (d, 6.8)	0.912 (d, 6.8)	C-21 and C-27 assignment could be reversed
33	26ξ-deuterio-(25*R*)-	0.796	0.765	0.960 (d, 6.6)	hidden by 18 and 19	26 HD *vs.* 16 H integrates *ca.* 0.9–1.0
37	(25*R*)-5α-furost-20(22)-en-26-yl acetate	0.796	0.661	1.573 (s)	0.930 (d, 6.8)	2.029 (–$OCOCH_3$, s); 4.71 (16 H, octet, 11, 7.5, and 6); 2.44 (17 H, d, 10); 3.85 (26 H, m, 10 and 6); 3.97 (26 H, m, 10 and 6)

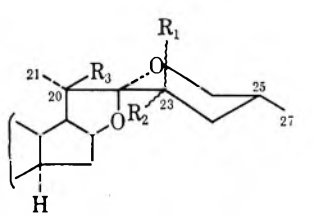
TABLE I
(*Continued*)

Compd no.	Description[b]	δ, ppm, from TMS: 19 H	18 H	21 H	27 H	Other H[c]
38	(25*R*)-5α-furost-20(22)-en-26-ol	0.79	0.67	1.58 (s)	0.93 (d, ~6)	($CDCl_3$[d]) 4.73 (16 H, octet, as in **37**); 2.46 (17 H, d, 10); ~3.40 (26 H); ~3.55 (26 H);
		0.766	0.750	1.652 (s)	1.102 (d, 6.6)	pyr C-18 and C-19 assignment could be reversed
39	(20*R*,25*R*)-5α-spirostan	0.783	0.931[e]	1.135[e] (d, 8.1)	0.778 (d, 5.7)	~2.0 (17 H, m); 2.42 (20 H, m);
40	20-acetyl-(20*R*,25*R*)-	0.776	0.994	1.343 (s)	0.774 (d, 5.6)	2.12 (–$COCH_3$, s); 2.83 (17 H, d, 6.5)
41	20-hydroxy-(20*S*,25*R*)-	0.779	0.924	1.356 (s)	0.796 (d, 6.0)	4.36 (–OH, s); 4.5 (16 H, m); 1.80 (17 H, d, 6.5); 3.6 (26 H, m)
42	$\Delta^{20(21)}$	0.785	0.672	5.07 (m, 16 and 2)	0.796 (d, 6.0)	4.58 (16 H, m); 2.65 (17 H, m, 7.5 and 2) (long range coupling to CH_2-21)
50	digallogenin (3β,15β-diol)	0.853	1.007	0.955 (d, 6.9)	0.798 (d, 5.9)	5.0 (15 H, m, 4 and 5.8)
52	3β-acetate 15-one	0.839	0.760	1.017 (d, 6.9)	0.775 (d, ~6)	2.000 (–$OCOCH_3$, s)
60	3β,12α-diol, Δ^{14}	0.867	1.112	1.002 (d, 6.5)	0.795 (d, 5.1)	(60 MHz) 2.7 (8 H, m); 5.53 (15 H, m); 4.9 (16 H, m)
61	3,12-dione, Δ^{14}	1.130	1.313	1.042 (d, 6.8)	0.798 (d, 5.7)	5.45 (15 H, m); 4.75 (16 H, m)
62	Δ^{14}	0.834	1.038	1.013 (d, 7.2)	0.788 (d, 5.5)	5.3 (15 H, m); 4.89 (16 H, m)
63	3-ethylene ketal, Δ^{14}	0.865	1.042	1.008 (d, ~7)	0.795 (d. 5.5)	5.3 (15 H, m); 3.90 ($2CH_2$ ketal, s); 4.89 (16 H, m)
64	(25*R*)-5α,14β-spirostan (**66**, 14β D)	0.756	0.965	0.974 (d, 6.4)	0.782 (d, 6.4)	
65	3-ethylene ketal, 14β H	0.784	0.966	0.971 (d, 6.7)	~0.78 (d, ~6)	3.90 (2 CH_2 ketal, s)
67	kryptogenin	0.803	1.038	1.053 (d, 6.6)	0.938 (d, 6.5)	5.342 (6 H, d, 4.5)

[a] All spectra were determined in deuteriochloroform (pretreated with anhydrous sodium carbonate) on a Varian Associates HA-100 nuclear magnetic resonance spectrometer (tetramethylsilane internal reference) unless otherwise noted. pyr = pyridine-d_5; s = singlet (not used in the case of 19 H and 18 H which are always singlets); d = doublet; m = multiplet. The value given after the letter "d" or "m" is the coupling constant, *J*, in hertz. Chemical shifts of all methyl resonances were determined with the counter incorporated in the instrument using an expanded scale. [b] All are derivatives of (25*R*)-5α-spirostan (**1**). Only the functionalities and/or changes of stereochemistry will be noted. [c] In most cases, the resonances for CH_2-26 and CH-16 are multiplets at δ 3.4 and 4.4, respectively. They will be denoted only if their chemical shifts are noteworthy. [d] Run with sodium carbonate in the tube. Immediately after an initial 250-sec sweep from which these data were obtained, a 500-sec sweep was run but showed that the compound had cyclized to **39** in the interim. Thus, even a mere *trace* of acid or even $CDCl_3$ itself catalyzes the cyclization. [e] The analagous known case of a downfield shift of a methyl resonance caused by steric crowding of one methyl group with another is the 0.076-ppm downfield shift of the C-19 resonance of cholestane upon addition of a 2β-methyl group. *Cf.* D. A. Schooley, Ph.D. Thesis, Stanford University, Stanford, Calif., 1968, p 42. [f] References 16e and 16g. [g] Reference 16f.



A, a, δ1.51
b, δ3.80



22, $R_1 = R_2 = D$; $R_3 = H$
23, $R_1 = R_2 = R_3 = D$
24, $R_1 = R_2 = H$; $R_3 = D$
25, $R_1 = D$; $R_2 = R_3 = H$

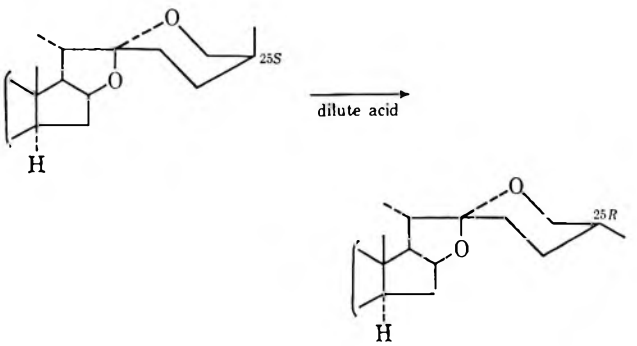
the spectrum of (25*R*)-5α-spirostan (**1**) has therefore been assigned[16a] (see also Table I), in part, to the protons at C-23. This signal was greatly reduced in intensity after acid-catalyzed exchange in deuterium-containing media.

Thus, when (25*R*)-5α-spirostan (**1**) was refluxed for 1 hr either in acetic acid-OD or in *ca.* 0.09 *N* DCl–EtOD with 1% D_2O, the 23,23-dideuterio analog **22** was obtained in 90% isotopic purity. Continued reflux gave 20,23,23-trideuterio-(25*R*)-5α-spirostan [**23** (the C-20 methyl doublet at 0.96[16g] collapsed to a singlet, δ 0.957)] which, upon mild back-exchange with acetic acid, afforded 20-deuterio-(25*R*)-5α-spirostan (**24**, 24% d_0, 75% d_1, 1% d_2).

As an additional check on the position of initial deuterium incorporation, the equatorial bromide **7** was reduced[23] with zinc in ethanol-OD to 23ξ-deuterio-(25*R*)-5α-spirostan (**25**, 93% d_1); the "spike" at δ1 .59 was found to decrease by 34%, whereas in the di-

deuterio analog **22** it decreased by 48%.[39] In a like manner, the 23,23-dibromide **5** was converted to the dideuterio derivative **22**.

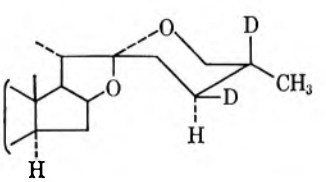
In an explanation of the "Iso-Reaction" originally discovered by Marker[40] in which a (25*S*)-spirostan is isomerized to a (25*R*)-spirostan by the action of dilute acid, Woodward proposed[41] an oxidation–reduction mechanism which, under acid-catalyzed exchange in



The Iso-Reaction[40]

deuterium-containing media, would require incorporation at C-25 as was noted by Callow.[36] Using an exchange procedure, a mass spectrometric method, and calculations all to be published elsewhere,[18a] we were able to confirm a 20% deuterium incorporation at C-25 under Callow's[36,18a] reaction procedure but, since deuterium at C-25 would collapse the C-27 doublet to a singlet, we must now prove that the acid-catalyzed exchange described above actually affords the C-20 deuterio analog **24** and not a C-25 isomer; that is, that the δ 0.96 collapsing doublet is, in fact, the resonance of C-21.

To do so, we made use of another approach to deuterium labeling of the spiroketal system, the homogeneous catalytic deuteration of the Δ^{24} olefin **9** since this procedure is known[42] not to involve isotopic scrambling in contrast to noble metal catalysts.[43] Using tris(triphenylphospho)rhodium chloride[42] in acetone solution, we obtained, in 97% isotopic purity, 24*S*,25*R*-dideuterio-(25*R*)-5α-spirostan (**26**), the nuclear



26

magnetic resonance spectrum of which showed a methyl doublet (J = 6.6 Hz) centered at δ 0.952 (C-21) and three methyl singlets: δ 0.758 (C-18), 0.790 (C-19), and 0.770 (C-27). This experiment provides unambiguous support for Kutney's[16g] conclusion that, of the two methyl doublets in the nmr spectrum of **1**, the 0.96-ppm doublet corresponds to the C-21 methyl group and that the one at 0.77 ppm is the C-27 methyl function.

In order to establish the configuration at C-25 in the dideuterio derivative **26**, use can be made of the extensive tables of Tori and Aono[16e] (Table II).

TABLE II

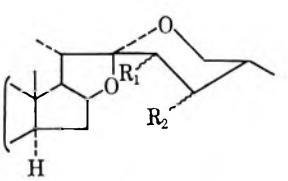
METEYL RESONANCES OF CERTAIN EXAMPLES OF THE NUCLEAR MAGNETIC RESONANCE SPECTRA OF STEROIDAL SAPOGENINS[16e]

Compd no.[a]	Substituents	C-25 stereochemistry	δ, ppm, from TMS 19 H	18 H	21 H	27 H
10	3β-acetate	*R*	0.83	0.77	0.96	0.78
11	3β-acetate	*S*	0.82	0.75	1.09	0.98
15	2α,3β-diol	*R*	0.87	0.77	0.96	0.79
16	2α,3β-diol	*S*	0.87	0.77	1.10	0.98
17	2α,3β-diacetate	*R*	0.93	0.76	0.95	0.78
18	2α,3β-diacetate	*S*	0.93	0.76	1.10	0.97

[a] Reference 16e.

Between each *R* and *S* pair, one notes that (a) C-21 is always downfield from C-27; (b) C-18 and C-19 do not shift; (c) in the *R* configuration, C-27 is always *between* C-18 and C-19 while, in the *S* configuration, it is always downfield from them; (d) in all cases, the substituents shift C-19 downfield from its position (δ 0.79) in (25*R*)-5α-spirostan (**1**). Thus, if the deuteration had produced a mixture or had given the 25*S* derivative, the differences would easily be discernible by a methyl singlet downfield from C-18 and C-19. No such signal was evident in the spectrum of **26**. Since *cis* addition is known to occur in homogeneous hydrogenation,[44] the stereochemistry at C-24 is assigned as *S* (equatorial deuterium as ring F is drawn in **26**).

(25*R*)-5α-Spirost-23-ene (**8**) was deuterated in the same manner giving 23ξ,24ξ-dideuterio-(25*R*)-5α-spirostan (**27**, 97% d_2) which, upon back-exchange in acetic acid, produced 24ξ-deuterio-(25*R*)-5α-spirostan (**28**, 98% d_1).



27, $R_1 = R_2 = D$
28, $R_1 = H$; $R_2 = D$

The foregoing data establish unequivocally that the monodeuterated derivative **24** is the 20-deuterio-(25*R*)-5α-spirostan and *not* the C-25 analog. Thus, the rate of acid-catalyzed exchange is C-23 >> C-20 >>> C-25.

Having effected deuterium introduction at positions 20, 23, 24, and 25, we next turned to C-26. For this

(39) A mere 13% decrease in the δ 1.59 spike in the spectrum of the C-20 deuterated analog **24** indicates that more than just the C-20 and C-23 protons have this chemical shift.

(40) R. E. Marker and E. Rohrmann, *J. Amer. Chem. Soc.*, **61**, 846 (1939). See also reference 8, p 818 ff.

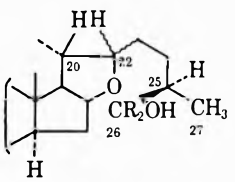
(41) See reference 37. When C-27 is substituted with an hydroxyl group, the reaction may go by a very simple mechanism (see reference 5f, p 765).

(42) W. Voelter and C. Djerassi, *Chem. Ber.*, **101**, 58 (1968), and references 2–8 therein.

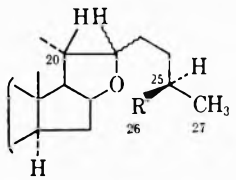
(43) C. Djerassi in "Proceedings of the Second International Congress on Hormonal Steroids," Excerpta Medica Foundation, Amsterdam, 1967, pp 261–268.

(44) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

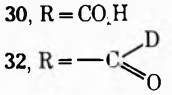
purpose, (25*R*)-5α-spirostan (**1**) was subjected to catalytic hydrogenation in glacial acetic acid with a trace of perchloric acid as promoter to afford[45] (20*S*,-22ξ,25*R*)-5α-furostan-26-ol (**29**)[46] which was oxidized[22] to (20*S*,22ξ,25*R*)-5α-furostan-26-oic acid (**30**) and then reduced with lithium aluminum deuteride to the 26,26-dideuterio alcohol **31**. Oxidation with Collins reagent[47] afforded 25-deuterio-(20*S*,22ξ,25*R*)-5α-furostan-26-al (**32**)[48] which was cyclized in acid[37,49] to 26ξ-deuterio-(25*R*)-5α-spirostan (**33**).



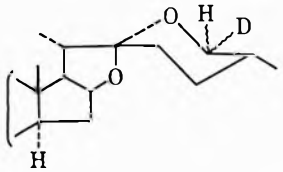
29, R = H
31, R = D



30, R = CO_2H



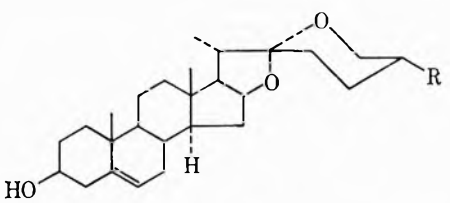
32, R = $-C(=O)D$



33

Deuterium labeling of steroidal angular methyl groups, especially of C-18[50] and C-19,[51] has, in the past, been difficult and in at least one case required total synthesis of the steroid.[50] Fortunately, the C-21 and C-27 labels have not proved so.

(25*S*)-Spirost-5-ene-3β,27-diol (**34**, "isonarthogenin")[52] was converted to the tosylate **35** which, upon displacement with lithium aluminum deuteride, gave 27-deuterio-(25*R*)-spirost-5-en-3β-ol (**36**, "27-deuteriodiosgenin"). Owing to the small amount of material



34, R = CH_2OH
35, R = CH_2OTs
36, R = CH_2D

with which we had to work, the hydroxyl group and the double bond in rings A and B were not eliminated. As such, this is the only labeled "final product" which is not a complete analog of (25*R*)-5α-spirostan (**1**).

In order to label C-21, we first converted (25*R*)-5α-spirostan (**1**) into (20*R*,25*R*)-5α-spirostan (**39**, "20-iso-3-deoxytigogenin") using Wall's[53] procedure (see Scheme II). The intermediates **37** and **38**, (25*R*)-5α-furost-20(22)-en-26-yl acetate and the corresponding alcohol, respectively, were not isolated during this procedure but were later prepared separately using acetic anhydride–pyridine with monomethylamine hydrochloride as catalyst.[54] Of the side products **40** and **41**, formation of the former has precedence in the literature.[55]

Chromium trioxide oxidation[56] of **39** to the alcohol **41**, followed by dehydration[55] to (25*R*)-5α-spirost-20-ene (**42**) and homogeneous catalytic deuteration[42] afforded 20,21-dideuterio-(20*R*,25*R*)-5α-spirostan (**43**)[57] which gave 21-deuterio-(25*R*)-5α-spirostan (**44**, 98% d_1) after gentle reflux in dilute hydrochloric acid–ethanol.[58]

The work so far described has provided a deuterium label for all nuclear positions in rings E and F peculiar to steroidal sapogenins. We now turn to rings C and D of the conventional steroid skeleton.

Desulfurization of thioketals with Raney nickel–deuterium is known[21] to be a conventional method of replacing a carbonyl function by two deuterium atoms, although the isotopic purity is frequently rather poor.[43] The sapogenin spiroketal is sensitive to some reagents used to catalyze the thioketal formation[49a] but Fieser's use[59] of perchloric acid avoids this difficulty. Any olefin formed upon reduction[60] can be eliminated with the use of silica gel containing silver nitrate in preparative thin layer chromatography.[61] It is upon these facts that the synthesis of the three deuterated analogs **47**, **49**, and **57** is based.

Thus, conversion of (25*R*)-5α-spirostan-12-one (**45**)[62] to the ethylene thioketal **46** and desulfurization with deuterio Raney nickel gave 12,12-dideuterio-(25*R*)-5α-spirostan (**47**) containing nearly equal amounts of d_1 and d_2 species. In a similar manner, after the ketone **45** was exchanged in deuteriomethanol containing sodium deuterioxide[21] to give the 11,11-dideuterio analog **48**, conversion to the thioketal and desulfurization with regular Raney nickel produced 11,11-dideuterio-(25*R*)-5α-spirostan (**49**) of high isotopic purity (91% d_2).

It is most fortunate that there are naturally occurring

(45) Reference 36, p 2648.

(46) The trivial name[18] for this system is "dihydropseudogenin," *e.g.*, "dihydro-3-deoxypseudotigogenin" (**29**).

(47) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(48) There is some question about the stereochemistry at C-25 in this case. Woodward[37] claims that the product is a mixture of the 25*R* and 25*S* species. Inversion of the original stereochemistry could occur under acidic[37] or basic conditions (abstraction of the proton at C-25). Thin layer chromatography did show a major and minor product but no attempt was made to separate them since the next step, acid cyclization, should give the same product or product mixture from either compound.

(49) (a) C. Djerassi, O. Halpern, G. R. Pettit, and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959). (b) Note that III in Woodward's mechanism[37] is the protenated form of the aldehyde **32**. The mechanism for this cyclization is thus given in reference 37, starting with III, and reading to the left.

(50) L. Tökés, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.* **90**, 5465 (1968).

(51) C. Djerassi and M. A. Kielczewski, *Steroids*, **2**, 125 (1963).

(52) References 5b,e. We wish to express our gratitude to Dr. Yuzo Nakagawa, Shionogi and Co., Osaka, Japan, for a sample of this material.

(53) M. E. Wall and H. A. Walens, *J. Amer. Chem. Soc.*, **77**, 5661 (1955).

(54) We thank Dr. Monroe E. Wall, Research Triangle Institute, Durham, N. C., for helpful discussion in this matter.

(55) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964).

(56) (a) M. E. Wall and H. A. Walens, *J. Amer. Chem. Soc.*, **80**, 1984 (1958); (b) M. E. Wall, H. A. Walens, and F. T. Tyson, *J. Org. Chem.*, **26**, 5054 (1961).

(57) Though we could have passed directly from **37** to **41**,[56b] it is fortunate that we did not since **39** provided a mass spectrum[18a,b] both quantitatively and qualitatively different from that of **1**. In addition, micro thin layer chromatography (see the Experimental Section) gave an easy differentiation between **1** and **39** (as well as **42**) which afforded a quick solution to the stereochemistry of **43** and **44**.

(58) Reference 53, pp 5661 and 5664.

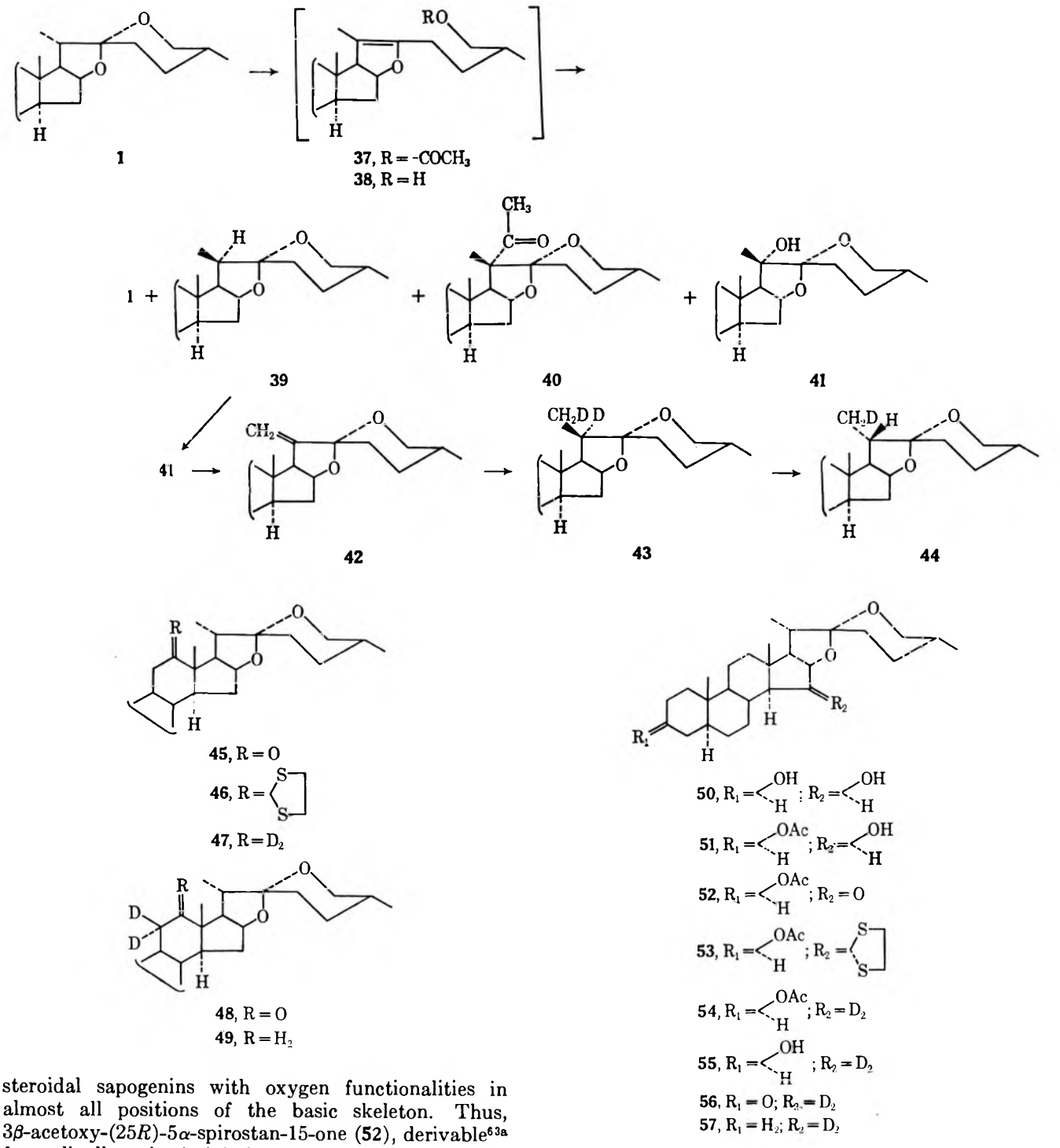
(59) D. L. Klass, M. Fieser, and L. F. Fieser, *J. Amer. Chem. Soc.*, **77**, 3829 (1955).

(60) C. Djerassi and D. H. Williams, *J. Chem. Soc.*, 4046 (1963).

(61) (a) E. Dunn and P. Robson, *J. Chromatogr.*, **17**, 501 (1965); (b) P. J. Stevens, *ibid.*, **36**, 253 (1968).

(62) M. E. Wall and S. Serota, *J. Amer. Chem. Soc.*, **78**, 1747 (1956).

SCHEME II



steroidal sapogenins with oxygen functionalities in almost all positions of the basic skeleton. Thus, 3β-acetoxy-(25*R*)-5α-spirostan-15-one (**52**), derivable[63a] from digallogenin (**50**)[63] through the acetate **51**, led, after appropriate deuterodesulfurization of its thioketal **53**, to the 15,15-dideuterio-3β-acetate **54**. Reduction of **54** with lithium aluminum hydride followed by conventional steps (**55** → **56** → **57**) gave 15,15-dideuterio-(25*R*)-5α-spirostan (**57**).

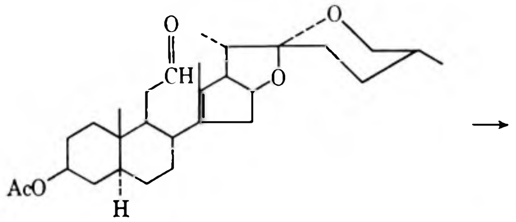
Since isotopic labeling of C-18 seemed to be accessible only through total synthesis and, hence, was not considered worthwhile, we were left with three unlabeled positions (C-14, C-16, and C-17) close to the spiroketal system. An obvious approach to C-14 and C-16, analogous to the method of preparation of the C-11 label **49**, is direct base exchange[21] of the ketone **52**. In fact, such an experiment showed (by mass spectrometric analysis)[18a] that the rate of exchange at C-14 is greater than at C-16 which would allow the selective production of either label by proper use of time and deuterated (for exchange) or nondeuterated (for back exchange) reagents. However, earlier studies in our laboratory[64] have shown that the C/D *cis* ring juncture (14βH) is more stable and the aforementioned exchange, therefore, gives a 14β-d_1 analog. The situation would not pose a problem except that attempted formation of

(63) (a) E. Bianchi, F. Girardi, F. Diaz, R. Sandoval, and M. Gonzales, *Ann. Chim.* (Rome), **53**, 1761 (1963); also see *Chem. Abstr.*, **60**, 12370*f* (1964); (b) R. Tschesche and G. Wulff, *Chem. Ber.*, **94**, 2019 (1961).

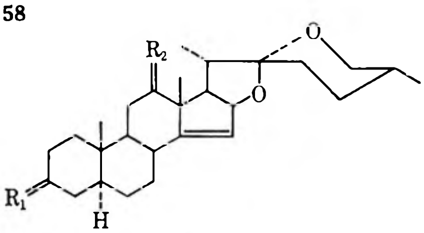
(64) C. Djerassi, T. T. Grossnickle, and L. E. High, *J. Amer. Chem. Soc.*, **78**, 3166 (1956); C. Djerassi, L. B. High, J. Fried, and E. F. Sabo, *ibid.*, **77**, 3673 (1955).

the corresponding 15-thioketal in the 14β series using the identical procedure employed in the preparation of **53** led to decomposition of the spiroketal side chain.

Labeling at C-14 was effected through the intermediacy of 12,13-seco-3β-acetoxy-(25*R*)-5α-spirost-13-en-12-one (**58**, "lumihecogenin acetate")[20b,c,65] which



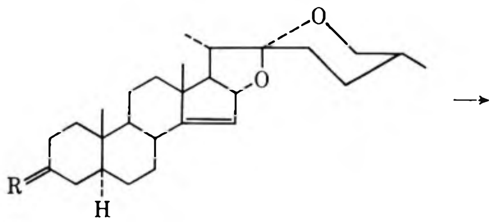
58



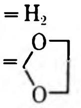
59, R_1 = <OAc, H ; R_2 = <H, OH

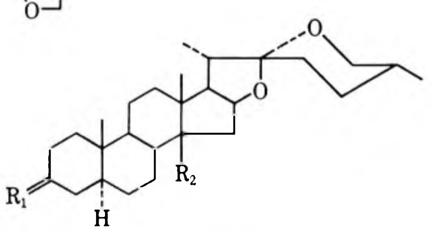
60, R_1 = <OH, H ; R_2 = <H, OH

61, R_1 = O; R_2 = O

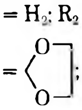


62, R = H_2

63, R = 



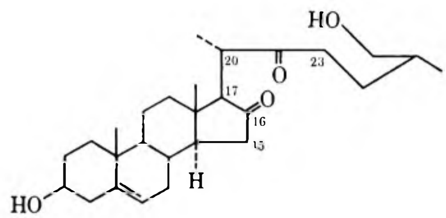
64, R_1 = H_2; R_2 = H

65, R_1 =  ; R_2 = H

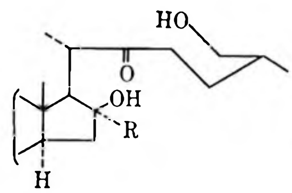
66, R_1 = H_2; R_2 = D

was transformed according to published[20b,c] procedures to 3β-acetoxy-(25*R*)-5α-spirost-14-en-12α-ol (**59**). Successive lithium aluminum hydride reduction to the diol **60**, Jones oxidation[22] to the diketone **61**, and Huang-Minlon reduction afforded (25*R*)-5α-spirost-14-ene (**62**)[66] which, upon deuteroboration with subsequent acid hydrolysis,[27,50] gave 14-deuterio-(25*R*)-5α,14β-spirostan (**66**) of acceptable isotopic purity.

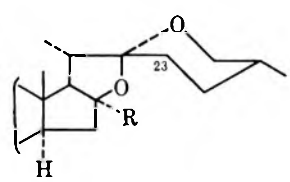
The introduction of the remaining C-16 and C-17 labels starts, in both cases, from the natural product kryptogenin (**67**). Sondheimer and collaborators have already reported[11] the selective reduction of the C-16 carbonyl group to the 16β-alcohol **68** (shown to exist as the 16,22-hemiketal)[70] with sodium borohydride in 2-propanol and subsequent acid cyclization to diosgenin (**36**, R = CH_3). Repetition of this sequence using deuterated reagents (sodium borodeuteride, 2-propanol-OD) afforded **69** and **70**, which, after catalytic hydrogenation of the 5,6 double bond, Jones oxidation,[22] and Huang-Minlon reduction gave 16-deuterio-(25*R*)-5α-spirostan (**71**, 73% d_1, 26% d_2, the extra deuterium being at C-23). The corresponding 20*R* compound **72** was prepared in the same manner[53] as the unlabeled species **39**.



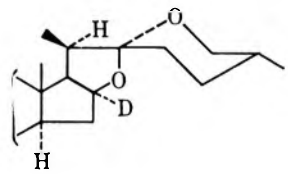
67



68, R = H
69, R = D



70, R = D
71, R = D, no unsaturation or oxygenation in rings A, B



72, C-20 isomer of **71**

Kryptogenin (**67**) also appeared to be the most suitable starting material for labeling C-17. Ex-

(65) We express our gratitude to Dr. Peter Blacon, University of Strathclyde, for a generous supply of this substance.

(66) Of the side products **63–65**,[67] the 3-ethylene ketals were surely formed during the first of two successive runs of the Huang-Minlon reduction in which ethylene glycol instead of diglyme was used as solvent.[68] The hydrogenated products arise due to diimide formation known[69] to occur under the strongly basic reaction conditions.

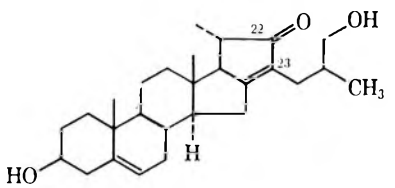
(67) The proof that the ethylene ketal of **63** and **65** is at C-3 and not at C-12 will not be detailed here. The nmr spectrum of both the C-3[18a] and C-12 ethylene ketal [Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 3722 (1964)] of (25*R*)-5α-spirostan were run and showed unequivocally that **63** and **65** are substituted as shown. In the case of **64**, compare the C-18 shift of the 14β isomer **64** and the 14α isomer **1** with the C-18 shift of 14β- and 14α-androstan (N. S. Bhacca and D. H. Williams, "Applications of nmr Spectroscopy in Organic Chemistry-Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1966, pp 19–24).

(68) W. H. F. performed initial small-scale studies on the sequence **59** → **60** → **61** but large-scale work on the sequence **59** → **62** was done by Dr. Erich C. Blossey in our laboratory in connection with another problem during his 1968 summer sabbatical leave from Rollins College, Winter Park, Fla.

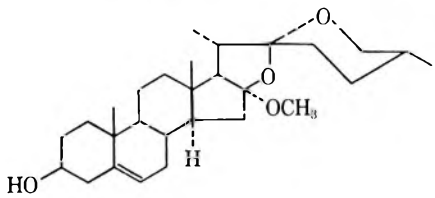
(69) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Lett.*, 347 (1961).

(70) St. Kaufmann and G. Rosenkranz, *J. Amer. Chem. Soc.*, **70**, 3502 (1948); F. C. Uhle, *ibid.*, **83**, 1460 (1961).

change at positions 15, 17, 20, and 23 of kryptogenin (**67**) followed by cyclization, as above, with undeuterated reagents and subsequent acid back-exchange of deuterium at C-20 and C-23 should yield a 15,15,17-trideuterio analog. In point of fact, that was the accomplished scheme except that the initial exchange could be done only with acetic acid-OD[71] on the diacetate of **67**. Exchange of kryptogenin with strong base (*e.g.*, NaOH) gives fesogenin (**73**)[4] and with hydrochloric acid in methanol, bethogenin (**74**).[4]

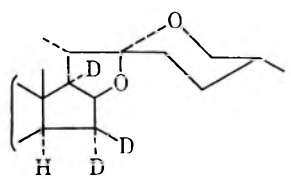


73



74

Thus, exchange of kryptogenin diacetate in refluxing acetic acid-OD followed by selective reduction[11] of the C-16 ketone to the corresponding alcohol, basic hydrolysis of the acetates, and acid cyclization gave 15,15,17-trideuterio-(25*R*)-spirost-5-en-3β-ol (**75**). The unsaturation and oxygenation in rings A and B was removed as described above in the preparation of the C-16 label to give 15,15,17-trideuterio-(25*R*)-5α-spirostan (**76**) of poor isotopic purity which, however, proved satisfactory for mass spectrometric purposes.[18a]



75, 5-en-3β-ol
76, no unsaturation or oxygenation in rings A, B

In summary, the present work describes, for the first time, procedures for extensive isotopic labeling of those positions of the steroidal sapogenin skeleton which differentiate it from the conventional steroids on which so much isotopic labeling has already been accomplished in our laboratory.[50,72] Virtually all of these procedures lend themselves to introduction not only of deuterium but also of tritium by substituting the appropriate reagents.

(71) Other reagents which we investigated were AcOD–DBr, $KHCO_3$–D_2O–EtOD, $KHCO_3$–D_2O–MeOD, D_3PO_4–DCl/D_2O, DCl–D_2O–$(CH_3)_2CHOD$.

(72) L. Tökés and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 5017 (1969).

Experimental Section[73]

Bromination of (25*R*)-5α-Spirostan[16a].—Bromine (324 mg) in benzene (3.5 ml) was added quickly to a solution of (25*R*)-5α-spirostan (**1**, 403 mg)[74] in benzene (50 ml) through which dry hydrogen bromide gas had been slowly bubbled for 5–10 sec both before and after addition; the reaction was kept in the dark and stirred at room temperature for 42 hr. Callow's procedure[16a] afforded 516 mg of an orange solid, separated by Rtlc twice with benzene (30)–*n*-hexane (70) to give three bands, average R_f 0.52, 0.41, 0.32 (band width *ca.* 0.08 on same scale).

The highest R_f material, recrystallized from acetone, afforded **23,23-dibromo-(25*R*)-5α-spirostan** (**5**, 99 mg): needles, mp 174–178.5° dec. A second Rtlc [three times, benzene (15%)–*n*-hexane (85%)] and two recrystallizations from acetone gave the analytical sample: needles; mp 185.5–186° (vac); ir_{max}^{KBr} practically identical with that of 23,23-dibromosapogenins in the literature;[75] $[\alpha]D$ −100° (*c* 0.755). (See Tables I and III for nmr data.)

Anal. Calcd for $C_{27}H_{42}Br_2O_2$: C, 58.07; H, 7.58; Br, 28.62; mol wt, 558.44. Found: C, 57.86; H, 7.57; Br, 28.39; mol wt, 556, 558, 560 ("triplet" from a Br_2, mass spec.).

The middle band (R_f 0.41) was identified as **23*R*-bromo-(25*R*)-5α-spirostan**[16f,76] (**6**, 69 mg): needles; mp 224–226° dec (acetone, change of form from 215–217°) (lit.[16f] mp 215–217° and mp 225–226°); ν_{max}^{KBr} 1168, 1090, 1071, 1040, 1018, 985, 971, 962, 910, 884, 854, 710, 691, 665 cm^{-1}; $[\alpha]^{26.8°}D$ −95° (*c* 0.970) (lit.[16f] −87.4°).

Anal. Calcd for $C_{27}H_{43}BrO_2$: C, 67.62; H, 9.04; Br, 16.66; mol wt, 479.53. Found: C, 67.54; H, 9.01; Br, 16.48; mol wt, 478, 480 ("doublet" from Br, mass spec.).

The lower band (R_f 0.32) yielded **23*S*-bromo-(25*R*)-5α-spirostan**[16f,76] (**7**, 132 mg): needles; mp 196.5–197° with decomposition (vac) (lit.[16f] 193–194°); ν_{max}^{KBr} 1175, 1054, 1010, 1002, 944, 914, 893, 862, 763, 730, 659 cm^{-1}; $[\alpha]^{26.3°}D$ −52.4° (*c* 0.667) (lit.[16f] −64.3°).

Anal. Calcd for $C_{27}H_{43}BrO_2$: C, 67.62; H, 9.04; Br, 16.66; mol wt, 479.53. Found: C, 67.61; H, 8.89; Br, 16.68; mol wt, 478, 480 ("doublet" from Br, mass spec.).

The original procedure,[23] modified to include fast addition of the bromine and ice-water quench after five min, affords a quantitative yield of a 1:1 mixture of **6** and **7**.

(25*R*)-5α-Spirost-23-ene (**8**).—To a stirred solution in a N_2 atmosphere of 23*R*-bromo-(25*R*)-5α-spirostan (**6**, 262 mg, 0.546 mmol) in dry benzene (25 ml) and DMSO (18.7 ml) was added

(73) Melting points were uncorrected and were determined on the Kofler block except for those labeled "vac" which were run in sealed, evacuated tubes. The infrared spectra were determined in chloroform, unless otherwise noted, on a Perkin-Elmer 421 grating spectrophotometer using sodium chloride cavity cells. Optical rotations, optical rotatory dispersion measurements, (Durrum-JASCO Model ORD-5 spectropolarimeter) and circular dichroism measurements (Durrum spectropolarimeter with CD attachment) were determined, unless othersise noted, in chloroform by or under direction of Mrs. R. Records. Nmr spectra (see Table I) were determined by Dr. Lois Durham and associates, notably Drs. M. Bramwell and T. Nishida. The mass spectra[18a] were measured by Mr. R. G. Ross and Dr. A. M. Duffield employing an A.E.I. MS-9 spectrometer (see ref 18a for details) Analytical thin layer chromatography [Atlc] was performed using microslides coated by dipping in chloroform/silica gel slurry; these were developed by spraying with 2% ceric sulfate in 2 *N* sulfuric acid followed by heat charring. Preparative thin layer [Ptlc] used a 1-mm-thick silica gel layer, the sample application method of Monteiro [H. J. Monteiro, *J. Chromatogr.*, **18**, 594 (1965)] and detection by "hot wire" [a simplified version of that of J. L. Bloomer and W. R. Eder, *ibid.*, **34**, 548 (1968)] and ultraviolet light. Solvent mixtures are given in parts per hundred. When repetition thin layer (Rtlc) was used, the number (N) of times the plate was run is denoted by NX. Silver nitrate plates[51] (10% of weight of silica gel) were detected by a thin strip of ceric sulfate solution which was heated by proximity to the hot wire. In all cases, silica HF-254 (E. Merck AG, Darmstadt) was used. All microanalyses were by Messrs. E. Meier and J. Consul.

(74) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **73**, 1528 (1951).

(75) Compare with M. E. Wall and H. W. Jones, *ibid.*, **79**, 3222 (1957). No acetate band at 1243 cm^{-1}, of course.

(76) Because of Atlc, we feel that our two 23-monobromospirostans are the most pure yet described. A private communication from Dr. J. C. Knight (see reference 16f), now at Arizona State University, Tempe, as well as samples kindly sent by him, indicate (Atlc) that their sample of the 23*S*-bromide is contaminated with the 23*R*; the latter is less soluble and, thus, would be precipitated first in a fractional crystallization. Our experience, in opposition to literature reports,[16f] has been that the 23*R* isomer will isomerize in solution, with a trace of acid, to the 23*S* isomer but that the reverse does not occur. Melting points are *not* a good criterion of purity.[16f]

potassium *t*-butoxide (245 mg, 2.18 mmol, *ca.* 0.05 *M* solution in base). After 90 min, the reaction was quenched by adding water, 1 ml 10% (aqueous) HCl, and ether.

The usual procedure gave a quantitative yield of **(25*R*)-5α-spirost-23-ene (8)**: flakes; mp 176.5–177.5° [chloroform (or ether)–methanol); ν_{max} 1650 (C=C), 1174, 1076, 980, 921, 878, 859 cm^{-1}; $[\alpha]^{25.2}$D −65.9° (c 1.001).

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62; mol wt, 398.61. Found: C, 81.03; H, 10.52; mol wt, 398 (mass spec.).

5α-Spirost-24-ene (9).—A solution of equal amounts of the 23-monobromides, **6** and **7**, (2.07 gm, 4.32 mmol), plus potassium *t*-butoxide (1.93 gm, 17.28 mmol, solution 0.35 *M* in base) in dry benzene (30 ml) and DMSO (20 ml) was initially stirred under nitrogen at 54° for 90 min after which the temperature was slowly raised to 90°. After 13 hr, the dark red solution was extracted with ether–10% HCl–water giving 1.5 g of a yellow oil. Column chromatography on Florisil (1:100) using increasing concentrations of benzene in *n*-hexane afforded (10–20% benzene) **5α-spirost-24-ene (9**, 762 mg, 46%): needles, spars, or fine clusters; mp 191.5–192° (vac, chloroform–methanol); ν_{max} (no C=C shows), 1175, 1159, 1068, 1009, 999, 977, 896, 887, 870 cm^{-1}; $[\alpha]$D −88.8° (c 1.002).

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62; mol wt, 398.61. Found: C, 81.14; H, 10.47; mol wt, 398 (mass spec.).

5α-Spirost-24-ene (9) from (25*R*)-5α-Spirost-23-ene (8).—(25*R*)-5α-Spirost-23-ene (**8**, 7.6 mg, 0.019 mmol) and potassium *t*-butoxide (9.2 mg, 4.3 molar excess) were slurried in dry DMSO (3 ml) and stirred at 107° in a nitrogen atmosphere. After 17 min, Atlc [benzene (70%) *n*-hexane (30%)] showed complete conversion to **5α-spirost-24-ene (9)**. Extraction with ether–very dilute HCl–water gave a quantitative yield of the trisubstituted olefin **9** whose structure was confirmed by mass spectrometry.[18a]

Epoxidation of (25*R*)-5α-Spirost-23-ene (8).—An approximately equimolar mixture of 23*S*-bromo(25*R*)-5α-spirostan (**7**) and (25*R*)-5α-spirost-23-ene (**8**, 500 mg, 1.26 mmol) was dissolved in chloroform (16.8 ml) to which was added 522 mg of *m*-chloroperbenzoic acid (min: 85% pure, 2.58 mmol; solution *ca.* 0.15 *M* in peracid). After stirring in the dark at room temperature for 79 hr, extraction with ether–carbonate afforded a semicrystalline solid (1.11 gm) separated by Rtlc [five times, benzene (70%)–*n*-hexane (30%)] to give (before crystallization) the bromide **7** (567 mg), a trace of the starting olefin **8** and the two epoxides: **23*R*,24*R*-epoxy-(25*S*)-5α-spirostan (10**, higher R_f isomer, 215 mg, 41%): needles and clusters: mp 203–206° (chloroform–methanol); ν_{max} 1157, 1068, 1040, 999, 971, 956, 880, 866, 820 cm^{-1}.

Anal. Calcd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21; mol wt, 414.61. Found: C, 78.29; H, 10.04; mol wt, 414 (mass spec.).

23*S*,24*S*-Epoxy-(25*S*)-5α-spirostan (11, lower R_f isomer, 136 mg): spars; mp 187–191° (ether–methanol); ν_{max} 1161, 1124, 1065, 1031, 994, 977, 958, 933, 880, 886, 840 cm^{-1}.

Anal. Calcd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21; mol wt, 414.61. Found: C, 78.22; H, 10.22; mol wt, 414 (mass spec.).

Epoxidation of 5α-Spirost-24-ene (9).—A solution of the olefin **9** (1.146 g, 2.88 mmol) and *m*-chloroperbenzoic acid (1.17 g, 2 molar excess) in chloroform (20 ml, 0.30 *M* in peracid, diluted to 40 ml, 0.15 *M*, after 1 hr) was stirred at room temperature in the dark for 24 hr and then treated as above. Careful column chromatography (activity III alumina, *n*-hexane through 50% benzene) gave the two epoxides. **24*S*,25*R*-epoxy-(25*R*)-5α-spirostan 12**, 494 mg, 41.5%, from *n*-hexane fractions only): needles; mp 242–244° (vac, chloroform–methanol); ν_{max} 1240, 1170, 1110, 1071, 1040, 1010, 970, 898, 873, 839 cm^{-1}; $[\alpha]^{25.2}$D −78.6° (c 1.005).

Anal. Calcd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21; mol wt, 414.61. Found: C, 77.92; H, 10.11; mol wt, 414 (mass spec.).

24*R*,25*S*-Epoxy-(25*S*)-5α-spirostan (13, 353 mg, 29.6%, fractions 10% through 50% benzene in *n*-hexane): flakes; mp 242–245° (vac, methylene chloride–ethanol or neat methanol); ν_{max} 1240, 1170, 1125, 1058, 1044, 1003, 970, 909, 877, 860, 813 cm^{-1}; $[\alpha]^{26.7}$D −69.6° (c 1.004).

Anal. Calcd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21; mol wt, 414.61. Found: C, 78.18; H, 10.12; mol wt, 414 (mass spec.).

TABLE III

EFFECTS OF SUBSTITUENTS IN RINGS D, E, AND F UPON THE POSITIONS OF THE METHYL SIGNALS IN (25*R*)-5α-SPIROSTANS

Substituent	Shift value, ppm[a] 19 H	18 H	21 H	27 H	Compd
Δ^{14} [b]	0.04	0.28	0.06	0.01	62
14β-H	−0.04	0.21	0.02	0.01	64
15β-OH[b]	0.03[c]	0.25[c]	0.00	0.02	50
15 keto[b]	0.00[d]	0.00[d]	0.06	0.00	52
$\Delta^{20(21)}$	−0.01	−0.09		0.02	42
20-d_1	0.00	0.02	−0.01[e]	0.02	24
20*R*-CH_3	−0.01	0.17	0.18	0.00	39
20*R*-acetyl	−0.02	0.23	0.40[e]	0.00	40
20*S*-OH	−0.02	0.16	0.40	0.02	41
Δ^{23}	0.01	0.04	−0.03	0.10	8
23*R*-Br[b]	0.00	0.04	0.22	0.03	6
23*S*-Br[b]	0.01	0.12	0.08	0.04	7
23,23-Br_2[f]	0.00	0.23	0.27	0.06	5
23*R*,24*R*-epoxy	0.01	0.07	−0.01	0.27	10
23*S*,24*S*-epoxy	0.01	0.09	0.04	0.22	11
23*R*-OH[b]	0.00	0.02	0.15	0.02	14
23*S*-OH[b]	0.01	0.04	−0.01	0.04	15
23 keto	0.00	0.01	−0.03	0.15	20
Δ^{24} [b]	0.00	0.02	0.05	0.82[e]	9
24*S*,25*R*-epoxy	0.00	0.00	0.00	0.50[e]	12
24*R*,25*S*-epoxy	−0.01	−0.01	−0.01	0.59[e]	13
24*S*-OH	0.01	0.01	0.02	0.15	16
24*R*-OH	0.00	0.00	0.00	0.09	17
24-keto	0.00	0.00	0.00	0.30	21
25*S*-OH	0.00	0.01	0.06	0.33[e]	18
25*R*-OH	0.00	0.00	0.01	0.51[e]	19
25-d_1	0.00	0.00	0.00	−0.01[e]	26

[a] Positive number indicates a downfield shift. Values are rounded to nearest hundredth ppm. Base values are the resonances of (25*R*)-5α-spirostan (**1**) (δ): 0.799 (19 H); 0.765 (18 H); 0.956 (21 H); ~0.776 (27 H). [b] Compare with the values given in reference 16e. [c] After subtracting the value due to the 3β-hydroxy group (see reference 16e). [d] After subtracting the value due to the 3β-acetoxy group (see reference 16e). [e] Singlet. [f] By direct measurement, not from addition of values from **6** and **7**.

Lithium Aluminum Hydride Reduction of the Epoxide 10.—23*R*,24*R*-Epoxy-(25*S*)-5α-spirostan (**10**, 62 mg) and lithium aluminum hydride (134 mg) were stirred for 24 hr in refluxing THF and the excess reagent decomposed with 1% (aqueous) HCl, followed by isolation of the product with ether affording 66 mg homogeneous material. Recrystallization from ether–methanol gave (25*R*)-5α-spirostan-23*R*-ol (**14**): mp 191–196°; ν_{max} 3584 (-OH), 1172, 1095, 1043, 1002, 975, 962, 939, 904, 861 cm^{-1}.

Anal. Calcd for $C_{27}H_{44}O_3$: mol wt, 416.62. Found: mol wt, 416 (mass spec.).

Lithium Aluminum Hydride Reduction of Epoxides 11, 12, and 13.—Similar reduction of epoxide **11** (26 mg) gave, after Rtlc [four times, EtOAc (10%)–*n*-hexane (90%), trace of pyridine], the following alcohols. **(25*S*)-5α-spirostan-24*R*-ol (17**, 13 mg): spars; mp 208.5–209.5° (vac, methylene chloride–methanol); ν_{max} 3490 (-OH, internal H bonding with ring-E oxygen), 1170, 1128, 1072, 1052, 1031, 1014, 990, 962, 918, 876, 850 cm^{-1}; $[\alpha]^{25.4}$D −79.6° (c 1.002).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65; mol wt, 416.62. Found: C, 78.12; H, 10.56; mol wt, 416 (mass spec.).

(25*R*)-5α-Spirostan-23*S*-ol (15, 4 mg before recrystallization): very fine needles; mp 163–168 (ether–methanol); ν_{max} 3560 (-OH), 1087, 1056, 1017, 996, 986, 956, 937, 909, 890, 855 cm^{-1}.

Anal. Calcd for $C_{27}H_{44}O_3$: mol wt, 416.62. Found: mol wt, 416 (mass spec.).

24*S*,25*R*-Epoxy-(25*R*)-5α-spirostan (**12**, 303 mg) gave only **(25*S*)-5α-spirostan-25-ol (18**, 264 mg crude yield, 86.8%): needles or plates; mp 172–4 (vac, methanol); ν_{max} 3575 (-OH), 1170, 1102, 1075, 1050, 1037, 973, 964, 933, 886, 844 cm^{-1}; $[\alpha]^{26.2}$D −73.7° (c 1.002).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65; mol wt, 416.62. Found: C, 77.69; H, 10.57; mol wt, 416 (mass spec.).

Reduction of 24*R*,25*S*-epoxy-(25*S*)-5α-spirostan (**13**, 244 mg), afforded, after column chromatography (activity II alumina 1:125, 50–50 benzene–*n*-hexane to neat benzene), (25*S*)-5α-**spirostan-24*R*-ol** (**17**, 112 mg before crystallization, 45.7%, see physical constants above) and (25*R*)-5α-**spirostan-25-ol** (**19**, 91 mg before crystallization, 38.0%): flakes; mp 174–177° (methanol); ν_{max} 3592 (–OH), 1171, 1133, 1058, 1028, 1017, 959, 917, 868, 843 cm^{-1}; $[\alpha]^{25.4}$D −74.0° (*c* 0.986).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65; mol wt, 416.62. Found: C, 77.42; H, 10.50; mol wt, 416 (mass spec.).

(25*R*)-5α-**Spirostan-23-one** (**20**).—Jones reagent[77] (0.1 ml, degassed with nitrogen) was added, in a nitrogen atmosphere, to a stirred ice-cold solution of the 23*R*-alcohol **14** (55 mg) in acetone (50 ml, $KMnO_4$ distilled). After 20 min, the reaction was quenched with 2-propanol and the product isolated with ether. Ptlc purification [benzene, trace pyridine] and two crystallizations from methylene chloride–methanol yielded (25*R*)-5α-spirostan-23-one (**20**): flakes; mp 196–198.5; ν_{max} 1730 (C=O), 1117, 1046, 1021 1001, 957, 912, 859, 850 cm^{-1}; ORD (*c* 0.070, dioxane), $[\alpha]_{589}$ −43°; $[\alpha]_{330}$ +472°; $[\alpha]_{280-282}$ −1127°; $[\alpha]_{255}$ −1042°; $[\alpha]_{240}$ −1212°; $[\alpha]^{27.3}$D −43° (*c* 0.070, dioxane, different determination from ORD).

Anal. Calcd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21; mol wt, 414.61. Found: C, 78.04; H, 10.12; mol wt, 414 (mass spec.).

In the same manner, the 23*S*-alcohol **15** (4 mg) was oxidized to the ketone **20** which was identified as the material described above by an identical infrared spectrum.

(25*S*)-5α-**Spirostan-24-one** (**21**).—A similar Jones oxidation[77] of (25*S*)-5α-spirostan-24*R*-ol (**17**, 13 mg) gave (25*S*)-5α-**spirostan-24-one** (**21**): needles and spars; mp 209–212° (methylene chloride–methanol); ν_{max} 1716 (C=O), 1155, 1054, 990, 954, 876 cm^{-1}; ORD (*c* 0.104, dioxane), $[\alpha]_{589}$ −76.8°; $[\alpha]_{312}$ −797°, trough; $[\alpha]_{305-303}$ −701°, shoulder; $[\alpha]_{274}$ +384°, peak; $[\alpha]_{240}$ +134°; $[\alpha]^{26.8}$D −59° (*c* 0.104, dioxane, different determination from ORD); $[\alpha]^{24.8}$D −73.9° (*c* 1.001, $CHCl_3$).

Anal. Calcd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21; mol wt, 414.61. Found: C, 78.28; H, 10.20; mol wt, 414 (mass spec.).

Lithium Aluminum Hydride Reduction of 24-Ketone (**21**).—Reduction in THF (3. 66 hr) of (25*S*)-5α-**spirostan-24-one** (**21**, *ca.* 14 mg) and purification by Ptlc [EtOAc (15%)–benzene (85%)] yielded mostly alcohol **17** (infrared and nmr comparison) together with a few mg of (25*S*)-5α-spirostan-24*S*-ol (**16**): ν_{max} 3590 (–OH), 1730 (trace of carbonyl), 1150, 1101, 1021, 978, 957, 875 cm^{-1}; for nmr see Table I. Calcd for $C_{27}H_{44}O_3$: mol wt, 416.62. Found: mol wt, 416 (mass spec.).

Acid-Catalyzed Exchange of (25*R*)-5α-**Spirostan** (**1**). **A. Deuterium Chloride**[78]**–Ethanol-OD.**[79]—A solution of (25*R*)-5α-spirostan (**1**, 100 mg)[74] and 9.2 *N* DCl–D_2O (0.5 ml) in ethanol-OD (50 ml) was refluxed for 1 hr and then allowed to stand at room temperature for 4 hr.[80] D_2O quenching of one-half the solution and extraction with ether–bicarbonate gave **23,23-d_2-(25*R*)-5α-spirostan** (**22**, 37 mg, 74%, after crystallization): mp 172–174° (ether–methanol); d_1 4%, d_2 90%, d_3 6%;[81] ν_{max} 1273, 1172, 1124, 1096, 1067, 1025, 998, 969, 906, 865, 821 cm^{-1}. The rest of the solution was refluxed for an additional 13 hr. Treatment as above gave an 88% recovery of **20,23,23-d_3-(25*R*)-5α-spirostan** (**23**), d_2 51%, d_3 49%; all "d_3" at C-20.[18a]

B. Acetic Acid-OD.[82]—(25*R*)-5α-Spirostan (**1**, 51 mg)[74] was refluxed in acetic acid-OD (6 ml) for 1 hr, cooled, and half of the solution was poured into water. Treatment as in part A (above) gave the d_2 **derivative** (**22**, d_1 9%, d_2 85%, d_3 6%).[83] A solution of (25*R*)-5α-spirostan (**1**, 303 mg)[74] in AcOD (50 ml) was refluxed for 168 hr, poured into ether, neutralized with sodium hydroxide and treated as above. Recrystallization (ether–methanol), Ptlc [EtOAc (15%)–*n*-hexane (85%)], sublimation [110°, 3 × 10^{-6} mm] and another recrystallization gave the d_3 **derivative** (**23**, 80 mg, mp 173.5–175°, d_1 14%, d_2 45%, d_3 41%) which, upon reflux in acetic acid-OH for 1 hr gave **20-d_1-(25*R*)-5α-spirostan** (**24**): d_0 24%, d_1 75%, d_2 1%; mp 172–175° (ether–methanol); ν_{max} 1257, 1235, 1151, 1055, 1010, 978, 910, 890, 860 cm^{-1}.

Reduction of 23*S*-Bromo-(25*R*)-5α-spirostan (**7**) **with Zinc and Ethanol-OD.**—A vigorously stirred mixture of the equatorial bromide **7** (201 mg) and dried zinc powder (808 mg) in ethanol-OD[79] (50 ml) was refluxed under nitrogen for 4 days and allowed to cool over a 12-hr period. The usual treatment provided **23ξ-d_1-(25*R*)-5α-spirostan** (**25**): mp 172–175° (ether–methanol); d_0 7%, d_1 93%; ν_{max} 1255, 1233, 1171, 1087, 1027, 978, 955, 892, 866, 856, 818 cm^{-1}.

Reduction of 23,23-Dibromo-(25*R*)-5α-spirostan (**5**) **with Zinc and Ethanol-OD.**—A mixture of the dibromide **5** (33 mg) and zinc dust (264 mg) in ethanol-OD[79] (16.5 ml) was refluxed for 3.5 days and treated as above. Ptlc [benzene] and then Rtlc [three times, benzene (50%)–*n*-hexane (50%)] afforded **23,23-d_2-(25*R*)-5α-spirostan** (**22**, 8 mg): mp 171–174° (ether–methanol) d_0 4%, d_1 52%, d_2 44%. Side products were not investigated.

24*S*,25*R*-d_2-(25*R*)-5α-Spirostan (**26**).—5α-Spirost-24-ene (**9**, 30.5 mg), tris(triphenylphosphine)rhodium chloride[42] (72.1 mg) and a magnetic stir bar were placed in an atmospheric hydrogenation flask and the system flushed well with deuterium gas. Acetone (10 ml) was introduced and the solution stirred with intermittent bubbling of deuterium through the clear, dark red liquid. After an initial few hours of stirring, a tan precipitate appeared which eventually turned black. After 4 days, Atlc [benzene (70%)–*n*-hexane (30%)] showed quantitative conversion to the saturated nucleus. The mixture was filtered, the solvent evaporated *in vacuo*, and the residue purified by Ptlc (benzene) to give, after crystallization, 24*S*,25*R*-d_2-(25*R*)-5α-spirostan (**26**, 12.5 mg): mp 170–172.4° (ether–methanol); d_2 97%, d_3 3%.

24ξ-d_1-(25*R*)-5α-Spirostan (**28**).—Similar homogeneous reduction of (25*R*)-5α-spirost-23-ene (**8**, 20.0 mg) gave **23ξ,24ξ-d_2-(25*R*)-5α-spirostan** (**27**, 6 mg, mp 171–173.6°; d_1 2%, d_2 97%, d_3 1%) which was refluxed in acetic acid-OH (2 ml) for 1 hr giving, after two recrystallizations from ether–methanol, **24ξ-d_1-(25*R*)-5α-spirostan** (**28**): mp 170–173°; d_1 98%, d_2 2%.

(20*S*,22ξ,25*R*)-5α-Furostan-26-ol (**29**).—(25*R*)-5α-Spirostan (**1**, 203 mg)[74] was hydrogenated in a Paar shaker at 32 psi for 71 hr over platinum dioxide (106 mg) in glacial acetic acid (40 ml) activated with 60% perchloric acid (5 drops). After filtration and extraction with ether–NaOH, the residue (224 mg) was subjected to basic hydrolysis and purified by Ptlc [EtOAc (30%)–benzene (70%), trace of pyridine] to give a 95% yield of (20*S*,22ξ,25*R*-5α-**furostan-26-ol** (**29**): mp 95–96° (sublimed); ν_{max} 3620 (–OH, free), 3415 (–OH, polymeric), 1163, 1094, 1033 (broad), 962 cm^{-1}; the normal sapogenin bands[14b,c] are entirely gone; $[\alpha]^{27.2}$D +5° (*c* 0.718 dioxane).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52; mol wt, 402.64. Found: C, 80.21; H, 11.27; mol wt, 402 (mass spec.).

26-d_1-(20*S*,22ξ,25*R*)-5α-Furostan-26-al (**32**).—Jones[77] oxidation of 145 mg of the alcohol **29** afforded (20*S*,22ξ,25*R*)-5α-**furostan-26-oic acid** (**30**) which was not further purified but reduced directly with lithium aluminum deuteride in THF. The resulting **26,26-d_2-(20*S*,22ξ,25*R*)-5α-furostan-26-ol** (**31**, 126 mg) was also used directly. Collins reagent (252 mg, 0.98 mmol)[47] in dry methylene chloride (10 ml) was added to a solution of the deuterated alcohol **31** (56 mg, 0.14 mmol) in the same solvent (6 ml) and stirred under nitrogen for 35 min. After filtration through silica (5% H_2O) to remove the reagent, the oxidation was repeated, as above, with 505 mg reagent giving a clear oil shown by Atlc [EtOAc (10%)–benzene (90%)] to be a two component mixture,[48] the main species of which was **26-d_1-(20*S*,22ξ,25*R*)-5α-furostan-26-al** (**32**, 33 mg), ν_{max} (mixture) 2058 (strong CD) and 1710 cm^{-1} (C=O).

(77) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(78) Deuterium chloride, 9.2 *N* in D_2O, was prepared by slow addition of D_2O to freshly distilled phosphorous oxychloride ($POCl_3$) with collection of evolved DCl in D_2O.

(79) A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

(80) Experiments have shown that exchange at room temperature is very slow compared with that at reflux.

(81) All values are calculated from data taken directly from the mass spectrum and are corrected for natural abundance of ^{13}C, ^{2}H, and ^{18}O.

(82) Prepared in 4-mol quantity according to G. Binsch and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 5157 (1965), by adding acetic anhydride (distilled from sodium) *to* an equimolar amount of D_2O: 99.1% AcOD; rest is unreacted anhydride with a trace of D_2O; –OD 99.9% (nmr).

(83) The other half of the solution was evaporated directly. The product showed the same isotopic composition, confirming that water does not adversely effect the label.

26ξ-d_1-(25R)-5α-Spirostan (33).—The deuterated aldehyde **32** (30 mg) was refluxed for 3 hr in absolute ethanol (20 ml) containing concentrated HCl (2 ml). After standing for 16 hr at room temperature, ether–carbonate extraction gave a quantitative yield of the cyclized sapogenin **33**. Further purification by Ptlc [benzene] and two crystallizations [ether–methanol] gave **26ξ-deuterio-(25R)-5α-spirostan (33)**: mp 160–162.5°; d_0 2%, d_1 97%, d_2 1%; ν_{max} 1200, 1152, 1063, 1044, 1021, 974, 961, 912, 879 cm^{-1}; nmr integral CH-16 *vs.* CHD-26 = 1.0/0.9.

27-d_1-(25R)-Spirost-5-en-3β-ol (36, 27-d_1-diosgenin).—Isonarthogenin-27-monotosylate[52] (**35**, 21 mg, prepared from 12.5 mg of the diol **34**[52]) was reduced with lithium aluminum deuteride in THF. The usual treatment and Rtlc [twice, EtOAc (20%)–benzene (80%)] to remove some diol, **34**, gave **27-d_1-(25R)-spirost-5-en-3β-ol (36)**: d_0 1%, d_1 90%, d_2 8%; d_3 1%.

Isomerization at C-20.[53] **(20R,25R)-5α-Spirostan (39).**—Using Wall's procedure,[53] (25R)-5α-spirostan (**1**, 2.3 gm)[74] was converted to the following mixture (crystallized yields), separated by Rtlc [twice, EtOAc (7%)–*n*-hexane (93%), trace of pyridine]; Starting material, **1** (15 mg, R_f 0.75). **(20R,25R)-5α-spirostan (39**, 674 mg, R_f 0.63): needles; mp 158–164°, 160–165° (ether–methanol), [lit.[62] mp 155–160°]; ν_{max} 1150, 1060, 1032, 999, 951, 914, 886, 849 cm^{-1}; $[\alpha]^{26}$D −57° (*c* 1.057) [lit.[62] −54° (dioxane, 25°)].

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07; mol wt, 400.62. Found: C, 80.90; H, 11.27; mol wt, 400 (mass spec.).

20-Acetyl-(20R,25R)-5α-spirostan (40, 307 mg, R_f 0.50): clusters; mp 220–223.5°; ν_{max} 1700 (C=O), 1154, 1140, 1059 1038, 1005, 981, 960, 920, 896, 874, 860 cm^{-1}; CD (*c* 2.78, dioxane), $[\theta]_{320}$ = 0°; $[\theta]_{280}$ = −830°; $[\theta]_{240}$ = 0°; $[\alpha]^{27.9}$D −77° (*c* 1.128).

Anal. Calcd for $C_{29}H_{46}O_3$: mol wt, 442.66. Found: mol wt, 442 (mass spec.).

(20S,25R)-5α-Spirostan-20-ol (41, 24 mg, R_f 0.35) was identified by infrared and mass spectral comparison with the same compound produced in an established way[53,66] (see below).

(25R)-5α-Furost-20(22)-en-26-yl acetate (37).[54]—To a refluxing solution of (25R)-5α-spirostan (**1**, 202 mg)[74] dissolved in a 1:1 mixture (10 ml) of pyridine–acetic anhydride was added, in a nitrogen atmosphere, methylamine hydrochloride (340 mg, recrystallized from absolute ethanol and dried) and reflux continued for 4.5 hr. The solvents were evaporated *in vacuo* and the remaining dark red sludge taken up in methylene chloride which was washed with brine and water, dried ($MgSO_4$), and evaporated *in vacuo*. Ptlc [EtOAc (5%)–benzene (95%) plus 2 drops of pyridine–100 ml solution] afforded a trace of the starting material **1** together with **(25R-5α-furost-20(22)-en-26-yl acetate (37)** which could not be crystallized but which was sublimed (117°, 1 × 10^{-5} mm): mp 69–71° (change of form from powder to microcrystals, mp 79°); ν_{max} 1727 (C=O), 1693 (C=C),[14d] 1243, 1032, cm^{-1}; $[\alpha]^{26.2}$D +20 (*c* 0.175, dioxane).[91]

Anal. Calcd for $C_{29}H_{46}O_3$: mol wt, 442.66. Found: mol wt, 442 (mass spec.).

Saponification of **37** gave **(25R)-5α-furost-20(22)-en-26-ol (38)**, ν_{max} 1685 cm^{-1} (C=C),[14d] no spiroketal peaks (**38** is very acid sensitive.)

Anal. Calcd for $C_{27}H_{44}O_2$: mol wt, 400.62. Found: mol wt, 400 [mass spec., which also shows a trace of impurity at M$^+$ − 14 (386)].

(20S,25R)-5α-Spirostan-20-ol (41).—Using Wall's procedure,[56a] (20R,25R)-5α-spirostan (**39**, 562 mg) was converted to (20S, 25R)-5α-spirostan-20-ol (**41**, 185 mg): flakes; mp 186–188° (ether–methanol); ν_{max} 3480 (–OH), 1151, 1064, 1015, 999, 988, 916, 870 cm^{-1}; $[\alpha]^{25.4}$D −80° (*c* 0.946).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65; mol wt, 416.62. Found: C, 77.90; H, 10.63; mol wt, 416 (mass spec.).

(25R)-5α-Spirost-20-ene (42).—Following known procedure,[56] the alcohol **41** (250 mg) was dehydrated to **(25R-5α-spirost-20-ene (42**, 107 mg, crystals): fine needles, mp 166–168° (ether–methanol); ν_{max} 3084, 1818, 1667 (C=C); 1159, 1063, 1039, 1018, 986, 966, 922, 902, 864 cm^{-1}; $[\alpha]^{24.8}$D −90° (*c* 0.992).

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62; mol wt, 398.61. Found: C, 81.37; H, 10.60; mol wt, 398 (mass spec.).

21-d_1-(25R)-5α-Spirostan (44).—As in the preparation of compound **26**, the olefin **42** (20 mg) was homogeneously reduced[42] to **20,21-d_2-(20R,25R)-5α-spirostan (43**, d_1 26%, d_2 68%, d_3 6% (mp 158–162° from ether–methanol) which was isomerized[58] in refluxing 1% HCl–ethanol (3 ml) to **21-d_1-(25R)-5α-spirostan (44)**, 98% d_1.

(25R)-5α-Spirostan 12-Ethylene Thioketal (46).—The 12-ketone **45** (71 mg) was dissolved in ethanedithiol, to which was added one drop of 60% perchloric acid,[59] and stirred for 4.5 hr after which a little methanol was added. Extraction with ether–5% KOH gave, after crystallization, **(25R)-5α-spirostan 12-ethylene thioketal (46**, 41 mg, 49%): very fine spars; double reproducible mp 197–201.5 and 203–204 (ether–methanol); ν_{max} (no carbonyl) 1157, 1094, 1067, 1048, 1005, 979, 961, 918, 894, 857 cm^{-1}; $[\alpha]^{27.3}$D −34.3° (*c* 0.992).

Anal. Calcd for $C_{29}H_{46}O_2S_2$: mol wt, 490.79. Found: mol wt, 490 (mass spec.).

12,12-d_2-(25R)-5α-Spirostan (47).—Deuterio Raney nickel (prepared from 1.5 g of Raney nickel catalyst powder)[60,84] in ethanol-OD[79] (40 ml) was added to the ethylene thioketal **46** (10 mg) and the mixture was refluxed under nitrogen for 17 hr after which it was filtered and the solvent evaporated *in vacuo*. The residue, a white solid, was crystallized from ether–methanol giving crystalline material (6 mg, mp 170–172°) which was further purified on silver nitrate Ptlc[61] [benzene (50%)–*n*-hexane (50%)] giving **12,12-d_2-(25R)-5α-spirostan (47**, 2 mg, analytical sample); mp 171–173.5° (ether–methanol); d_0 4%, d_1 44%, d_2 49%, d_3 3%. (Infrared essentially the same as that of **1**.)

11,11-d_2-(25R)5α-Spirostan (49).—(25R)-5α-Spirostan-12-one (**45**, 10 mg),[62] dissolved in a nitrogen atmosphere in a solution composed of methanol-OD[79] (10 ml), D_2O (5 ml), and sodium (*ca.* 200 mg) was refluxed for 27 hr and extracted with ether–water. The residue, after Ptlc [EtOAc (15%)–benzene (85%)], was crystallized from acetone to give an analytical sample of **11,11-d_2-(25R)-5α-spirostan-12-one (48)**: mp 196–198.5° (lit.[62] 193–199°); d_1 3%, d_2 95%, d_3 2%. As in the preparation of **46**, the filtrate from this material was converted, in quantitative yield, to **11,11-d_2-(25R)-5α-spirostan-12-one 12-ethylene thioketal.** This residue was dissolved in ethanol (15 ml) to which was added W-2 Raney nickel (*ca.* 200 mg). After refluxing for 10.5 hr and standing overnight, the reaction was filtered, the solvent evaporated *in vacuo*, and the residue purified on silver nitrate Ptlc[60,84] [benzene], then Rtlc [twice, benzene (50%)–*n*-hexane (50%)] to give **11,11-d_2-(25R)-5α-spirostan (49**, ether–methanol): Rtlc [benzene (70%)]–*n*-hexane (30%)], d_0 1%, d_1 8%, d_2 91%.

3β-Acetoxy-(25R)-5α-spirostan-15-one 15-Ethylene Thioketal (53).—The 15-oxo-3β-acetate **52** (118 mg)[63] was converted, as described for **46**, to **3β-acetoxy-(25R)-5α-spirostan-15-one 15-ethylene thioketal (53**, 118 mg, 86%): needles; mp 254–256° (ether–methanol); ν_{max}^{KBr} 1728 (C=O, acetate), 1178, 1145, 1129, 1108, 1054, 1024, 977, 952, 907, 893, 862; 790, 737, 721, 687, 659, 604 (C-S); $[\alpha]^{26.6}$D −92.8° (*c* 0.973).

Anal. Calcd for $C_{31}H_{48}S_2O_4$: C, 67.84; H, 8.82; S, 11.68; mol wt, 548.82. Found: C, 67.79; H, 8.79; S, 11.74; mol wt, 548 (mass spec.).

15,15-d_2-(25R)-5α-Spirostan (57).—The thioketal **53** (79 mg) was converted to **3β-acetoxy-15,15-d_2-(25R)-5α-spirostan (54**, structure confirmed by spectral comparisons[14c] using the same procedure as for the preparation of **47**. Lithium aluminum hydride reduction of **54** (58 mg) in ether to the alcohol **55** and Jones oxidation[77] of 33 mg of this material gave the corresponding ketone **56** which showed a large amount of olefinic impurity. Wolff-Kishner reduction,[50] silver nitrate Ptlc[61,73] (benzene), and crystallization from ether–methanol gave **15,15-d_2-(25R)-5α-spirostan (57)**: mp 168–172.5°; d_1 34%, d_2 59%, d_3 7%.

Base-Catalyzed Exchange of 3β-Acetoxy-(25R)-5α-spirostan-15-one (52).—In a typical exchange, 179 mg **52** in 50 ml of methanol-OD[79] with 1.2 gm of sodium was refluxed for 39 hr and then extracted with ether–brine–water. The residue was purified by Rtlc [four times, EtOAc (20%)–benzene (80%) with 2 drops of pyridine–100 ml solvent] and sublimed 135–140° (10^{-6} mm), to give **3β-hydroxy-14,16-d_2-(25R)-5α,14β-spirostan-15-one** (134 mg): mp 186–189.5° (lit.[63] 181–183°). The position and amount of exchange can be obtained from consideration of several peaks in the mass spectra[18a] of the exchange products (Table IV).

(25R)-5α-Spirost-14-ene-3β,12α-diol (60).—The acetate **59**[20c] (1.18 gm) was reduced by refluxing 1 hr in dry ether (250 ml) with lithium aluminum hydride (1 g). The usual procedure gave **(25R)-5α-spirost-14-ene-3β,12α-diol (60)**: large flat prisms; no distinct melting point (two separate preparations), softens and goes clear over range 100–125°; ν_{max} 3600 (–OH), 3050 and 1640 (C=C), 1155, 1122, 1098, 1058, 1032, 1008, 975, 956, 915, 893, 858 cm^{-1}; $[\alpha]^{25.7}$D +59.2° (*c* 1.004).

(84) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2091 (1963).

TABLE IV

Sample	Exchange time hr	Molecular ion[a] d_0	d_1	d_2	d_3	C-16 d_0	d_1	d_2
1	0.5 (EtOD)	18[b]	57	26		71	29	
2	12.5 (EtOD)	8	56	34	2	63	37	
3	39 (MeOD)		4	95	1	1	98	1

[a] Includes, of course, both C-14 and C-16 labels. The incorporation may actually be better than calculated. See E. Lund, H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Amer. Chem. Soc.*, 85, 1528 (1963). [b] 4% of "d_0-1" species.

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83; mol wt, 430.61. Found: C, 75.00; H, 10.07; mol wt, 430 (mass spec.).

(25*R*)-5α-Spirost-14-ene-3,12-dione (61).—Jones oxidation[77] of **60** gave a quantitative yield of **(25*R*)-5α-spirost-14-ene-3,12-dione (61)**, the analytical sample from ether–*n*-hexane: very fine spars: mp 209.5–213 or 212–214.5 (both with decomposition, depends on heating rate); $\nu_{max}^{CS_2}$ 3058 and 1642 (C=C), 1710 (C=O), 1178, 1117, 1061, 1042, 1010, 978, 958, 948, 919, 898, 860, 851 cm^{-1}; ORD (*c* 0.125, dioxane), $[\alpha]_{600}$ +64°; $[\alpha]_{589}$ +64°; $[\alpha]_{316}$ +1890° (peak); $[\alpha]_{310}$ +1695°; $[\alpha]_{306}$ +1780° (peak); $[\alpha]_{300}$ +1056° (shoulder); $[\alpha]_{296}$ +992° (shoulder); $[\alpha]_{275}$ +40°; $[\alpha]_{250}$ +1728°; $[\alpha]^{27}$°D +100° (*c* 1.040).

Anal. Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98; mol wt, 426.57. Found: C, 76.11; H, 9.27; mol wt, 426 (mass spec).

Huang-Minlon Reduction of (25*R*)-5α-Spirost-14-ene-3,12-dione (61).—Initially,[68] the dione **61** (467 mg) was dissolved in ethylene glycol (20 ml), anhydrous hydrazine (2 ml), and *n*-butyl alcohol (10 ml) and distilled for 1 hr, removing material up to a boiling point of 120°. The mixture was cooled and potassium hydroxide (2 g) added. Distillation was again started until reaching 130° with subsequent reflux at that temperature for 4 hr. Acid treatment gave a yellow oil (500 mg) containing three major components, none of whose R_f matched the starting material. The residue was dissolved in absolute ethanol (20 ml), diethylene glycol (50 ml), and anhydrous hydrazine (5 ml) and refluxed (103°) for 3 hr in an argon atmosphere. Upon cooling, potassium hydroxide (5.55 g) was added and the solution distilled until the temperature reached 210°. Reflux (4 hr), acid work-up (pH 1), and Ptlc (EtOAc (5%)–benzene (95%) trace pyridine] gave two 2-component mixtures. The one of greater R_f, after Rtlc [seven times, benzene (30%)–*n*-hexane (70%)] and silver nitrate Ptlc[61,73] [benzene (50%)–*n*-hexane (50%)], gave the following analytical samples.

(25*R*)-5α-Spirost-14-ene (62, R_f 0.40): plates; mp 116–117.5° (ether–methanol); ν_{max} 3055 and 1645 (C=C), 1174, 1156, 1133, 1056, 1004, 975, 957, 918, 894, 861 cm^{-1}; $[\alpha]^{26.4}$°D *ca.* −30° (*c* 0.069).

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62; mol wt, 398.61. Found: C, 81.31; H, 10.57; mol wt, 398 (mass spec.).

(25*R*)-5α,14β-Spirostan (64, R_f 0.54): needles; mp 131–132° (ether–methanol); ν_{max} 1170, 1076, 1054, 1013, 980, 958, 942, 919, 902, 862 cm^{-1} (different from the 14α analog, **1**, by direct comparison); $[\alpha]^{26.4}$°D −41° (*c* 0.201).

Anal. Calcd for $C_{27}H_{44}O_2$: mol wt, 400.62. Found: mol wt, 400 (mass spec.).

The second pair, after silver nitrate Ptlc[61,73] [EtOAc (10%)–benzene (90%)] gave **(25*R*)-5α-spirost-14-ene 3-ethylene ketal (63)**: rectangular plates; mp 150.5–153.5 (ether–methanol); ν_{max} 3050 and 1640 (C=C), 1170, 1151, 1128, 1089, 1056, 1001, 970, 940, 914, 906, 887, 857 cm^{-1}; $[\alpha]^{26.9}$°D +32° (*c* 0.497).

Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71; mol wt, 456.64. Found: C, 76.12; H, 9.63; mol wt, 456 (mass spec.).

(25*R*)-5α,14β-Spirostan 3-ethylene ketal (65): needles; mp 173–176.5° (ether–methanol); ν_{max} 1168, 1149, 1089, 1070, 1051, 1010, 979, 942, 916, 897, 882, 863 cm^{-1}; $[\alpha]^{26}$°D −36° (*c* 0.235).

Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11; mol wt, 458.66. Found: C, 76.15; H, 10.11; mol wt, 458 (mass spec.).

14-d_1-(25*R*)-5α,14β-Spirostan (66).—Deuterioborane,[50] generated[27] by the addition of sodium borodeuteride (161 mg) in dry diglyme (10 ml) to a stirred solution of boron trifluoride etherate (1.43 gm, freshly distilled) in dry diglyme (10 ml), was bubbled, in an argon atmosphere over a period of 17 min, into a stirred and cooled solution of (25*R*)-5α-spirost-14-ene (**62**, *ca.* 24 mg) in dry THF (30 ml). After an additional 13 min, the generation was repeated. The ice bath was removed after 1 hr total time and the solution stirred at room temperature for 11 hr. The reaction was then cooled to −81° (Dry Ice–acetone), propionic acid (1.5 ml, freshly distilled) added carefully, and the solution stirred for 1 hr. Upon return to room temperature, the THF was evaporated *in vacuo*, more propionic acid (10 ml) added, and the solution heated at 108–114° for 10 hr at which time it was extracted with ether–5% NaOH to give a mixture, a small part of which, by Atlc [20% silver nitrate, benzene (50%)–*n*-hexane (50%)], appeared to be the desired 14-deuterated analog of **1**. Purification by Rtlc [twice, benzene (50%)]–*n*-hexane (50%)] and again on a plate made by addition of 0.3% (w/w) rhodamine 6-G to the silica gel HF [four times, benzene (50%)–*n*-hexane (50%), uv detection] gave **14-d_1-(25*R*)-5α,14β-spirostan (66)**, identified as the 14β isomer by comparison of the nmr and of the quantitative aspects of the mass spectrum:[18a] ν_{max} 1138, 1074, 1050, 1012, 979, 964, 918, 897, 861 cm^{-1}; d_0 14%, d_1 79%, d_2 7%.

16-d_1-(25*R*)-5α-Spirostan (71).—Under an atmosphere of argon, sodium borodeuteride (50 mg) was added to kryptogenin (**67**, 131 mg) dissolved in 2-propanol-OD (30 ml). The flask was stoppered and the solution stirred for 19 hr giving, in part, the deuterated triol **69** which was not isolated. [That the cyclized product **70** was isolated after acid treatment is evidence for the existence of **69**.] After addition of a saturated solution of HCl gas in deuterium oxide[85] (2 ml) and 20 min stirring, the product was isolated with ether[11] and purified by Rtlc [twice EtOAc (30%)–benzene (70%)] giving 74 mg (ether–methanol) of **15-d_1-(25*R*)-spirost-5-en-3β-ol (74)** d_1 71%, d_2 28%, d_3 1%. This material (73 mg) was hydrogenated (Paar) at 49 psi for 4.5 hr in absolute ethanol (100 ml) over platinum dioxide (69 mg) and the resulting 3β-ol deoxygenated in the sequence Jones oxidation,[77] Wolff–Kishner reduction (see preparation of **62**, second run) to give **16-d_1-(25*R*)-5α-spirostan (71**, 10 mg): mp 171–173.5° (ether–methanol), d_1 73%, d_2 26%, d_3 1%; ν_{max} 1237, 1154, 1068, 1044, 1000, 972, 912, 885, 857 cm^{-1}.

16-d_1-(20*R*,25*R*)-5α-Spirostan (72).—16-d_1-(25*R*)-5α-Spirostan (**71**, 15 mg) was isomerized, as in the preparation[55] of **39**, to give a small amount of starting material together with **16-d_1-(20*R*,25*R*)-5α-spirostan (72)**: mp 156–163°[62]; d_0 21%, d_1 71%, d_2 8%.

15,15,17-d_3-(25*R*)-5α-Spirostan (90).—Kryptogenin diacetate[4] (**67**, as the diacetate, 1.00 gm) was refluxed for two consecutive 113-hr periods in acetic acid-OD to give an incorporation of d_2 6%, d_3 21%, d_4 33%, d_5 25%, d_6 10%, d_7 (?) 4%, d_8 (?) 1%, mp 148–149.5° (ether) (lit.[4] 152–153). This material (475 mg) was reduced in a manner analogous to the preparation of **71**, but using sodium borohydride and 2-propanol-OH. Saponification to the 3β,16β,27-triol with 10% sodium hydroxide, cyclization[11] with 6 *N* HCl (20 ml), ether[11] isolation and Rtlc [twice, EtOAc (30%)–benzene (70%)] gave the **15,15,17-d_3-(25*R*)-5α-spirost-5-en-3β-ol (75)**: mp 192–198° (lit.[86] 204–207°); d_0 5%, d_1 26%, d_2 29%, d_3 22% d_4 11%, d_5, 6%, d_6 1%.

The deuterated 5-en-3β-ol **75** was converted to the saturated, deoxygenated species (82 mg) by the series 69 hr hydrogenation (Paar, 46 psi, ethanol, equal weight PtO_2), Jones oxidation,[77] Wolff–Kishner reduction (see preparation of **62**, second part). Finally, 48 mg of the resulting material were refluxed in 1% ethanolic HCl for 70 hr and isolated with ether–carbonate affording, **15,15,17-d_3-(25*R*)-5α-spirostan (76)**: d_0 10%, d_1 30%, d_2 31%, d_3 21%, d_4 6%, d_5 2%.

Registry No.—**1**, 5012-14-6; **5**, 24744-26-1; **6**, 4988-84-5; **7**, 4947-69-7; **8**, 24744-29-4; **9**, 24744-30-7; **10**, 24744-31-8; **11**, 24744-32-9; **12**, 24744-33-0; **13**, 24744-34-1; **14**, 24744-35-2; **15**, 24744-36-3; **16**, 24744-37-4; **17**, 24744-38-5; **18**, 24744-39-6; **19**, 24744-40-9; **20**, 24744-41-0; **21**, 24744-42-1; **22**, 5380-66-5; **23**, 24744-44-3; **24**, 24744-45-4; **25**, 24744-46-5; **26**, 24744-47-6; **27**, 24744-48-7; **28**, 24744-49-8; **29**, 24744-50-1; **32**, 24744-51-2; **33**, 24744-52-3; **37**, 24744-53-4; **38**, 24744-54-5; **39**, 24799-49-3; **40**, 24799-50-6; **41**,

(85) H_2O should have been used here since the acidic solution produced an incorporation of 28% deuterium at C-23. (Position determined by mass spec. fragmentation[18a].)

(86) Merck Index, 7th ed, p 378.

24742-73-2; **42**, 24742-74-3; **43**, 24742-75-4; **46**, 24742-76-5; **47**, 24742-77-6; **50**, 6877-35-6; **52**, 24742-79-8; **53**, 24742-80-1; **57**, 24742-81-2; **60**, 24742-82-3; **61**, 24742-83-4; **62**, 24742-84-5; **63**, 24799-51-7; **64**, 24742-85-6; **65**, 24742-86-7; **66**, 24742-87-8; **67**, 468-99-5; **71**, 24742-89-0.

Terpenoids. LXVII.[1] Chemical Studies of Marine Invertebrates. VII.[2] Interrelation of Seychellogenin and Lanosterol through Lanostane-3β,11β,18-triol[3]

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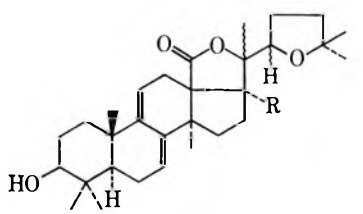
Seychellogenin (**9**) and lanosterol (**10**) were chemically correlated through a common intermediate, lanostane-3β,11β,18-triol (**21**). Seychellogenin was reduced to the triol **11**, whose 3,18-diacetate (**12**) was dehydrated and then hydrogenated to give a mixture of C-20 epimers of **15**. Subsequent chromium trioxide oxidation to the ene–dione **16**, followed by zinc reduction to **17** and removal of the C-7 functionality, gave 11-oxolanostane-3β,18-diol diacetate (**20**) and its C-20 epimer **19**. Reduction of **20** provided the desired triol **21**. Lead tetraacetate–iodine oxidation of 11β-hydroxylanostan-3β-yl acetate (**22**) and immediate reduction with lithium aluminum hydride yielded the 11β,18 ether **24** and the 11β,19 ether **25**. The former was oxidized to the lactone **27** and then reduced to the triol **21**, which was identical with the product of natural origin. The 11β,19 ether (**25**) was converted to lanostane-3β,11β,19-triol (**37**) which could be correlated with the known 11β,19-cyclolanostane-3β,11α-diol 3-acetate (**23**).

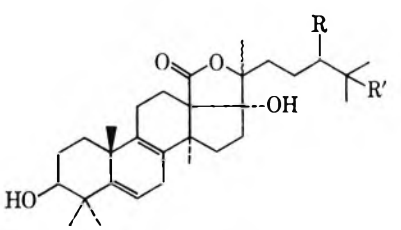
In recent years a number of triterpenoid saponins of toxic nature have been isolated from many species of sea cucumbers in the family *Holothuroidea* of the phylum *Echinodermata*. The first successful structural work was accomplished on the saponin mixture from the Cuvier glands of the Caribbean species *Actinopyga agassizi*.[5] Acid hydrolysis of the mixture yielded monosaccharides, sulfuric acid, and a mixture of triterpenoid aglycones, among them 22,25-oxidoholothurinogenin (**1**) and its deoxy analog **2**. In the saponin, an aglycone was found to be bound directly to a chain of four monosaccharides and to a sulfate ester. Enzymatic hydrolysis studies[6] have also led to some interesting speculations about the true nature of the triterpenoid portion when attached to the monosaccharide chain and the sulfate ester residue.

Chemical studies by our group established the structure of yet another aglycone, griseogenin (**3**), as an acid hydrolysis product from the body walls of the Brazilian sea cucumber *Halodeima grisea L.*[7] Structures **4** and **5** for the two sapogenins stichopogenin A_2 and stichopogenin A_4 from the Far Eastern sea cucumber *Stichopus japonicus* were assigned mainly on the basis of spectral evidence.[8]

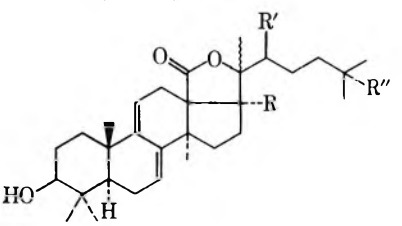
Thus all sea cucumber aglycones appear to possess a similar lanostane skeleton with structural variations in the side chain. Chemical and spectroscopic evidence all pointed to the correctness of the postulated struc-



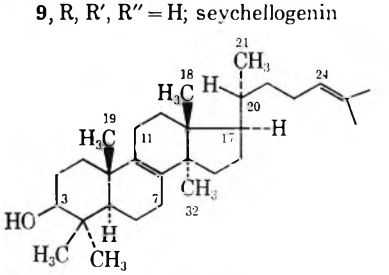
1, R = OH
2, R = H



4, R, R′ = double bond
5, R = H; R′ = OH



3, R, R′ = OH; R″ = H
6, R, R′ = H; R″ = OH
7, R, R′ = H; R″ = OMe
8, R = OH; R′ = H; R″ = OMe
9, R, R′, R″ = H; seychellogenin



10, lanosterol

(1) For part LXVI, see P. Roller and C. Djerassi, *J. Chem. Soc. C*, 1089 (1970).

(2) For part VI, see B. Tursch, R. Cloetens, and C. Djerassi, *Tetrahedron Lett.*, 467 (1970).

(3) Financial assistance from the National Institutes of Health Grant No. GM-06840 is gratefully acknowledged.

(4) (a) Taken in part from the Ph.D. Thesis of P. R., Stanford University, 1969; (b) Postdoctoral research associate, on leave from the Free University of Brussels, Brussels, Belgium.

(5) J. D. Chanley, T. Mezzetti, and H. Sobotka, *Tetrahedron*, **22**, 1857 (1966).

(6) J. D. Chanley and C. Rossi, *ibid.*, **25**, 1897, 1911 (1969).

(7) B. Tursch, I. S. deSouza Guimaraes, B. Gilbert, R. T. Aplin, A. M. Duffield, and C. Djerassi, *ibid.*, **23**, 761 (1967).

(8) G. B. Elyakov, T. A. Kuznetsova, A. K. Dzizenko, and Yu. N. Elkin, *Tetrahedron Lett.*, 1151 (1969).

tures, which, however, remained to be proved through a direct chemical correlation with lanosterol itself. Such occasion arose in our continuing study of marine toxins when we isolated[2,9] several new aglycones on acid hydrolysis of the saponins of the Indian Ocean sea cucumber *Bohadschia koellikeri*, namely koellikerigenin (**6**), ternaygenin (**7**), and praslinogenin (**8**) from the body walls, and seychellogenin (**9**) from the Cuvier glands. All were structurally related.

Seychellogenin (**9**), $C_{30}H_{46}O_3$, revealed the presence of a five-membered lactone ring (1755 cm^{-1}), one tertiary methyl group on an oxygen-bearing carbon (δ 1.40, CH_3-21), six additional methyl groups, one equatorial secondary hydroxyl group (δ 3.23, CH-3) which could be acetylated (δ 4.5), two vinylic protons (δ 5.25 and 5.56, CH-7 and CH-11), and a heteroannular diene (λ_{max} 237, 244, 252 nm; ϵ 11,000, 12,000, and 8000) commensurate with such a chromophore when contained in the fused-ring system of agnosterol.[10] The remaining four degrees of unsaturation are satisfied by structure **9**, containing four fused carbocyclic rings. Thus, seychellogenin appears to be the simplest possible holothurinogenin, being devoid of substituents on the side chain and lacking the hydroxyl group on C-17.

Seychellogenin was therefore chosen as the most convenient aglycone for an attempted chemical correlation with lanosterol (**10**), both because of its relative abundance in the particular species and because of its suitable structure. When compared with 24,25-dihydrolanosterol, the most distinguishing feature of seychellogenin appeared to be its functionalized character at carbon atoms 18 and 20. Our approach called for the derivation of a common intermediate from both seychellogenin and lanosterol using unambiguous chemical steps. Such an intermediate was obtained by removal of functionality of C-20[11] in a suitable derivative of seychellogenin as well as the conversion of its skeletal unsaturation to an 11-hydroxy derivative. At the same time lanosterol could be converted to an 11-hydroxy intermediate according to established methods[12,13] and subsequent application of one of the intramolecular hydrogen abstraction reactions[14] on the latter resulted in the introduction of functionality on C-18. The preparation of such a 3,11,18-trifunctionalized derivative from both sources is detailed below.

Seychellogenin (**9**) on lithium aluminum hydride reduction in tetrahydrofuran gave the triol **11**, which on acetylation under the usual conditions furnished the triol 3,18-diacetate **12** (Scheme I). Both substances were acid sensitive and their formulation is consonant with their spectral data.

Dehydration of the triol diacetate **12** with phosphorus oxychloride in pyridine gave a mixture of double-bond isomers;[15] separation of the two major olefins, **13** and **14**, was achieved in approximate yields of 35% each. The more polar $\Delta^{20(21)}$ isomer **13** was characterized by broad singlets at 4.75 and 4.87 ppm in the nmr spectrum corresponding to the two olefinic protons on C-21. In the case of the less polar $\Delta^{20(22)}$ olefin **14**, the vinylic methyl group (C-21) appeared as a broad three-proton singlet at 1.65 ppm.

Catalytic hydrogenation of either olefin **13** or **14** in ethyl acetate over platinum oxide gave a mixture of C-20 epimers **15** without affecting the skeletal unsaturation, as attested by its ultraviolet spectrum, λ_{max} 235, 242, and 251 nm. It is appropriate to remark at this stage that, while the dehydrogenation step leading to olefins **13** and **14** destroyed the asymmetric center on C-20, subsequent hydrogenation produced an approximately equal mixture of C-20 epimers, one of which had to possess the same configuration as lanosterol.

The epimeric mixture **15** on oxidation with chromium trioxide in acetic acid yielded the expected ene–dione **16**, with an ultraviolet absorption, λ_{max} 271 nm (ϵ 7080), characteristic for such a chromophore.[12] Zinc reduction of the unsaturated diketone **16** in refluxing acetic acid gave in good yield the saturated diketone **17**. The two C-20 epimeric components could be barely distinguished on silica gel chromatoplates, and separation was not attempted at this stage. Removal of the 7-keto function was achieved by conversion to the 7-ethylene thioketal **18** followed by Raney Nickel desulfurization in refluxing ethanol. The product could be well separated into two components by preparative tlc. The less polar isomer was assigned the 11-oxo-20-epilanostane-3β,18-diol diacetate (**19**) structure while the more polar isomer corresponded to the natural epimer, 11-oxolanostane-3β,18-diol diacetate (**20**) as shown by its eventual correlation with lanosterol. The spectral data were in agreement with the assigned structures in that both epimers showed the expected infrared carbonyl band at 1737 cm^{-1} corresponding to the two ester functions and a low frequency band at 1700 cm^{-1} assigned to the C-11 carbonyl substituent.[16] The two-proton singlet at 4.00–4.02 ppm in the nmr spectrum of both epimers corresponded to the 18-acetoxymethylene protons and the two singlets at 1.13 and 1.08 ppm were assigned to methyls 19 and 32.[17] Furthermore, the spectra of both epimers exhibited an interesting pair of doublets at 2.45 and at 2.65 ppm, each integrating for one proton (J = 14 Hz). While in the well-studied case of 5α-androstan-11-one[18] the 12α and 12β protons appeared indistinguishable (A_2 singlet) at 2.27 ppm, the 18-acetoxy substituent in our case introduces sufficient molecular asymmetry to differentiate the C-12 axial and equatorial protons. Also, a broad low field doublet (J = 14 Hz), centered at 2.85 ppm, was tentatively assigned to the C-1 equatorial proton. Molecular models show that this γ-hydrogen atom lies in the nodal plane of the C-11 carbonyl group. Such paramagnetic shifts have ample precedent in the litera-

(9) For preliminary communication, see P. Roller, C. Djerassi, R. Cloetens, and B. Tursch, *J. Amer. Chem. Soc.*, **91**, 4918 (1969).

(10) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, England, 1964, p 51.

(11) The plan of removal of the C-18 functionality from a derivative of seychellogenin was abandoned after preliminary work on the preparation and the reductive removal of the 18-tosylate, -iodide, and hydrazone derivatives indicated undue difficulties: see R. Cloetens, Ph.D. Thesis, Brussels, 1969.

(12) W. Voser, M. Montavon, H. H. Gunthard, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **33**, 1893 (1950).

(13) J. F. McGhie, M. K. Pradhan, and J. F. Calvalla, *J. Chem. Soc.*, 3176 (1952).

(14) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, 525 (1964).

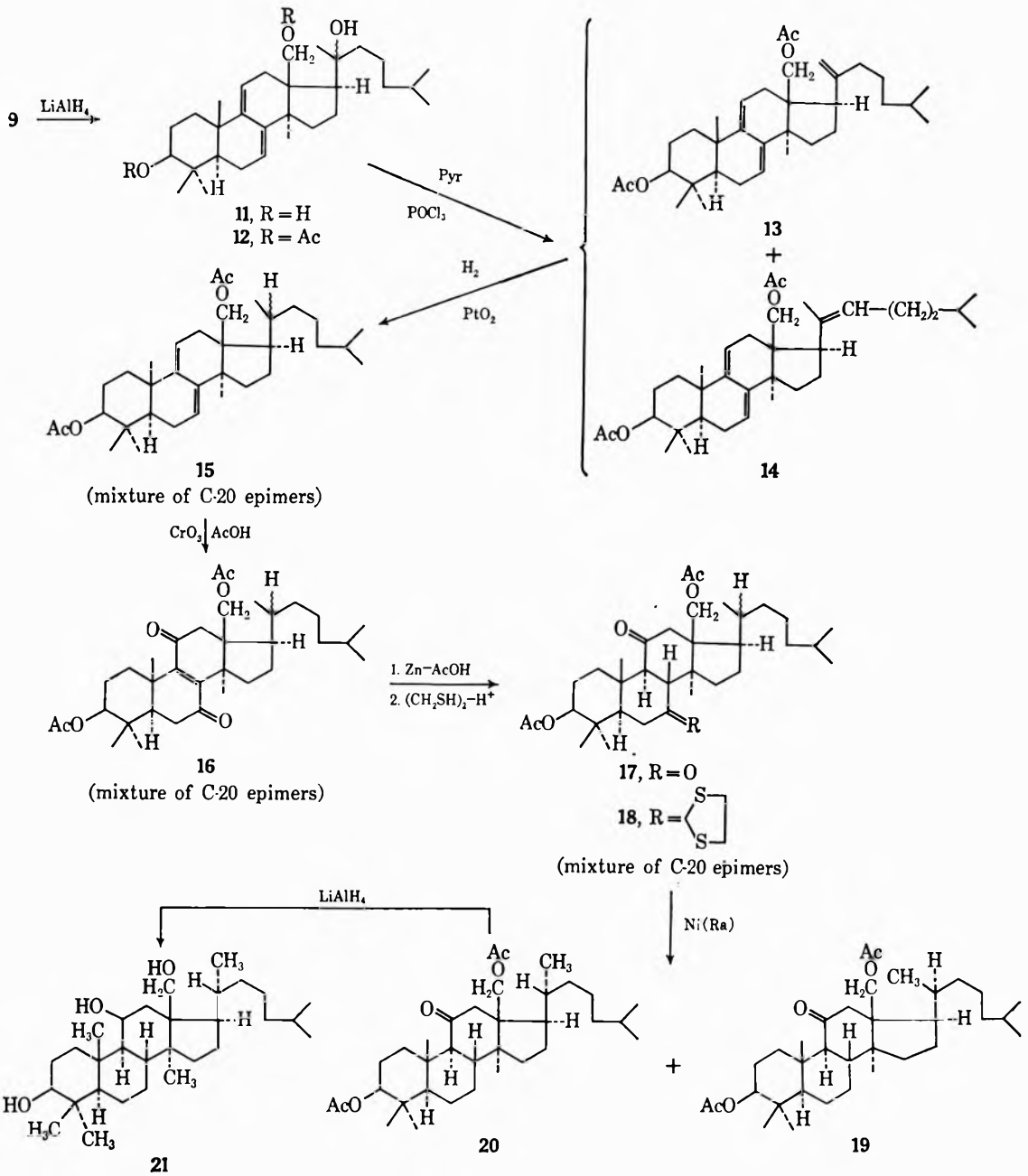
(15) J. S. Mills, *J. Chem. Soc.*, 2196 (1956).

(16) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 435.

(17) F. Hemmert, B. Lacoume, J. Levisalles, and G. R. Pettit, *Bull. Soc. Chim. Fr.*, 976 (1966); F. Hemmert, A. Lablanche-Combier, B. Lacoume, and J. Levisalles, *ibid.*, 982 (1966).

(18) D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2810 (1963).

SCHEME I



ture.[15,19] The principal mass spectral fragment (*m/e* 361) from the two epimeric ketones **19** and **20** can be rationalized in exact analogy to the well-studied case of 5α-androstan-11-one.[20]

Lithium aluminum hydride reduction of the more polar 11-keto-3,18-diacetate **20** gave on sublimation the sought after lanostane-3β,11β,18-triol (**21**), mp 228–229°. The spectral data are in full agreement with the structural assignment and will be detailed later.

The conversion of lanosterol to a 3,11,18-functionalized derivative was performed next. 11β-Hydroxylanostan-3β-yl acetate (**22**) was selected as the starting material and was prepared from lanosterol according to the method of Voser, *et al.*[12] Several methods were considered for the functionalization of the C-18 angular methyl group. Radical-type reactions involving intramolecular attack by an 11-oxy radical on a suitably located nonactivated carbon have been advantageously utilized in recent years to synthesize C-18 and/or C-19 substituted steroids.[14,21,22] However, in the case of the lanostane derivatives, both the photocyclization of the 11-ketolanostane[23,24] and the isomerization of the 11β-nitrite[25,26] yielded exclusively C-19 substituted products, which were not useful for our synthetic ob-

(19) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry, Illustrations from the Steroid Field," Holden-Day, San Francisco, Calif., 1964, p 66.

(20) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2091 (1963).

(21) R. H. Hesse in "Advances in Free-Radical Chemistry," Vol. III, G. H. Williams, Ed., Academic Press, New York, N. Y., 1969.

(22) M. Akhtar in "Advances in Photochemistry," Vol. 2, W. A. Noyes, G. S. Hammond, and J. N. Pitts, Ed., Academic Press, New York, N. Y., 1964.

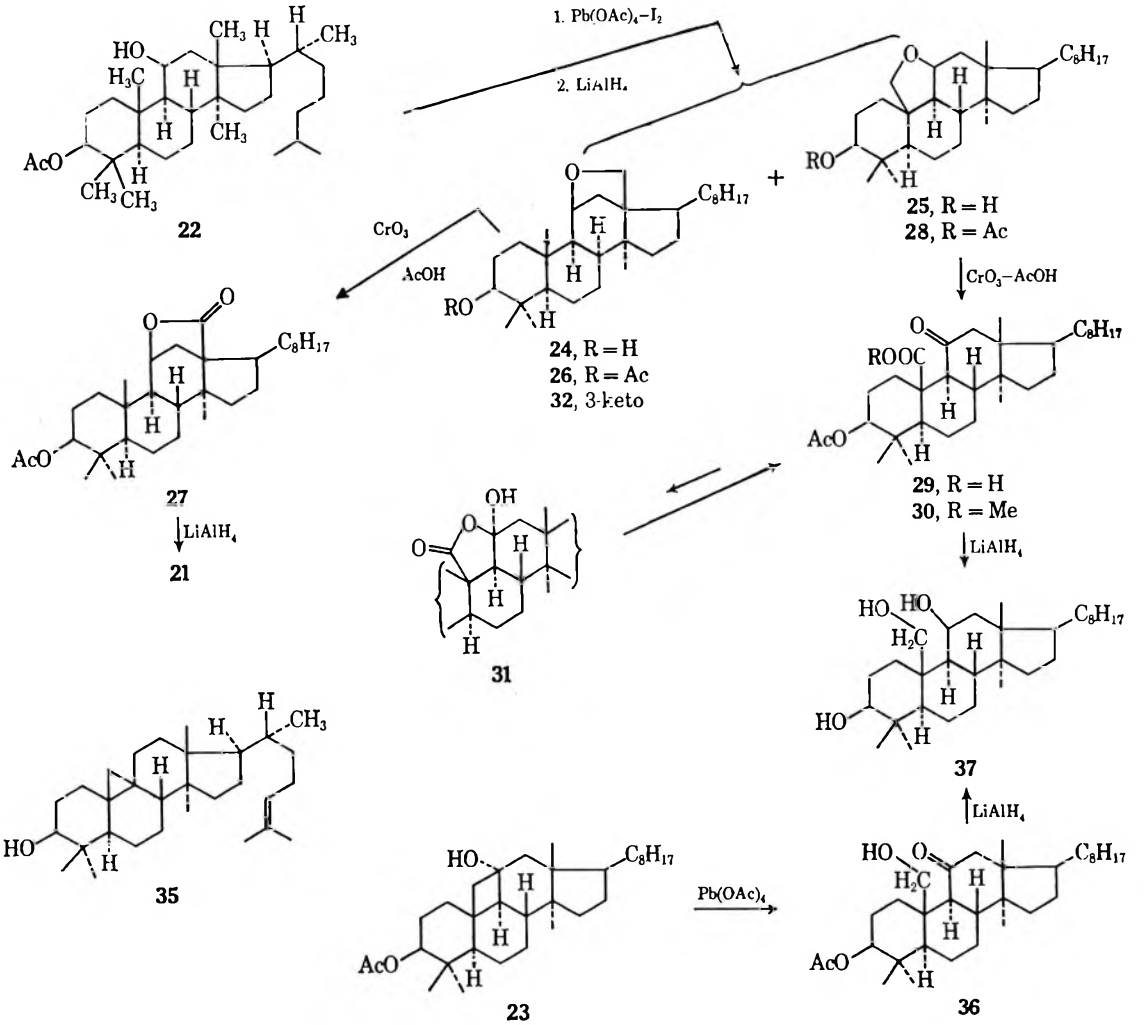
(23) R. Imhof, W. Graf, H. Wehrli, and K. Schaffner, *Chem. Commun.*, 852 (1969).

(24) E. Altenburger, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **48**, 704 (1965).

(25) D. H. R. Barton, D. Kumari, P. Wetzel, L. J. Danks, and J. F. McGhie, *J. Chem. Soc. C*, 332 (1969).

(26) D. H. R. Barton, R. P. Budhiraja, and J. F. McGhie, *ibid.*, 336 (1969).

SCHEME II



jectives. Our choice of the proper reagent was lead tetraacetate. Oxidations with this reagent on 11β-hydroxy steroids have been reported[27] to give mainly the 11-keto derivative (54%) and in addition small quantities of the 11β,19, 11β,18, and 1β,11α ethers. The Swiss group also found[28] that in the presence of iodine the above reaction produces a complex mixture of presumably ethers, α-iodo ethers, and hemiacetals in which C-18 and C-19 were attacked to about equal extent and after silver acetate oxidation the corresponding ethers and hemiacetals were isolated in 5–10% yields each.

In our envisaged synthetic sequence, it seemed advantageous to reduce the products of multiple attack, such as iodo ethers, to ethers and the overoxidized components, such as hemiacetals, to polar triols immediately after lead tetraacetate–iodine treatment. Thus, refluxing 11β-hydroxylanostan-3β-yl acetate (**22**) with lead tetraacetate and iodine in cyclohexane–acetic acid under illumination followed by lithium aluminum hydride reduction gave a mixture that could be easily separated into an ether-containing fraction and into more polar fractions containing mixtures of polyols. Preparative tlc of the ether-containing fraction gave two components identified as 11β,18-epoxylanostan-3β-ol (**24**) and 11β,19-epoxylanostan-3β-ol (**25**) in 32 and 8% overall yields, respectively. Acetylation of **24** followed by oxidation of the acetate **26** with chromium trioxide in acetic acid gave the corresponding lactone **27** in 35% yield. On the other hand, the oxidation of 11β,19-epoxylanostan-3β-yl acetate (**28**) resulted in formation of acidic material formulated as **29**. The latter on esterification with diazomethane gave 3β-acetoxy-11-oxolanostan-19-oic acid methyl ester (**30**). Aside from the analytical data, spectrocsopic information was available to support the structural assignments.

The oxo acid **29**, obtained by chromium trioxide oxidation of the 11β,19-epoxy acetate **28**, exhibited no lactone absorption around 1760 cm^{-1} in the infrared spectrum in chloroform, thus excluding the presence of a cyclized form such as **31**. Furthermore, the presence of an intense band at 1708 $^{-1}$, assigned to the 11-keto function,[16] confirms the observation that in fact the oxo acid **29** is entirely in the open form in solution. See Scheme II.

The nmr spectra of the 11β,18-ether alcohol **24**, its acetate **26**, and its 3-keto derivative **32** exhibit a two-proton singlet at 3.63–3.67 ppm, attributable to the methylene protons on C-18. By comparison, the analogous protons of 11β,18-epoxy-5α-pregnane-3β,20β-diol diacetate (**33**) have been found[27] to appear nonequivalent, illustrating the effect of the nearby 20-acetate group. On the other hand, the C-19 methylene

(27) K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963).

(28) J. Kalvoda, K. Heusler, G. Anner, and A. Wettstein, *ibid.*, **46**, 618 (1963).

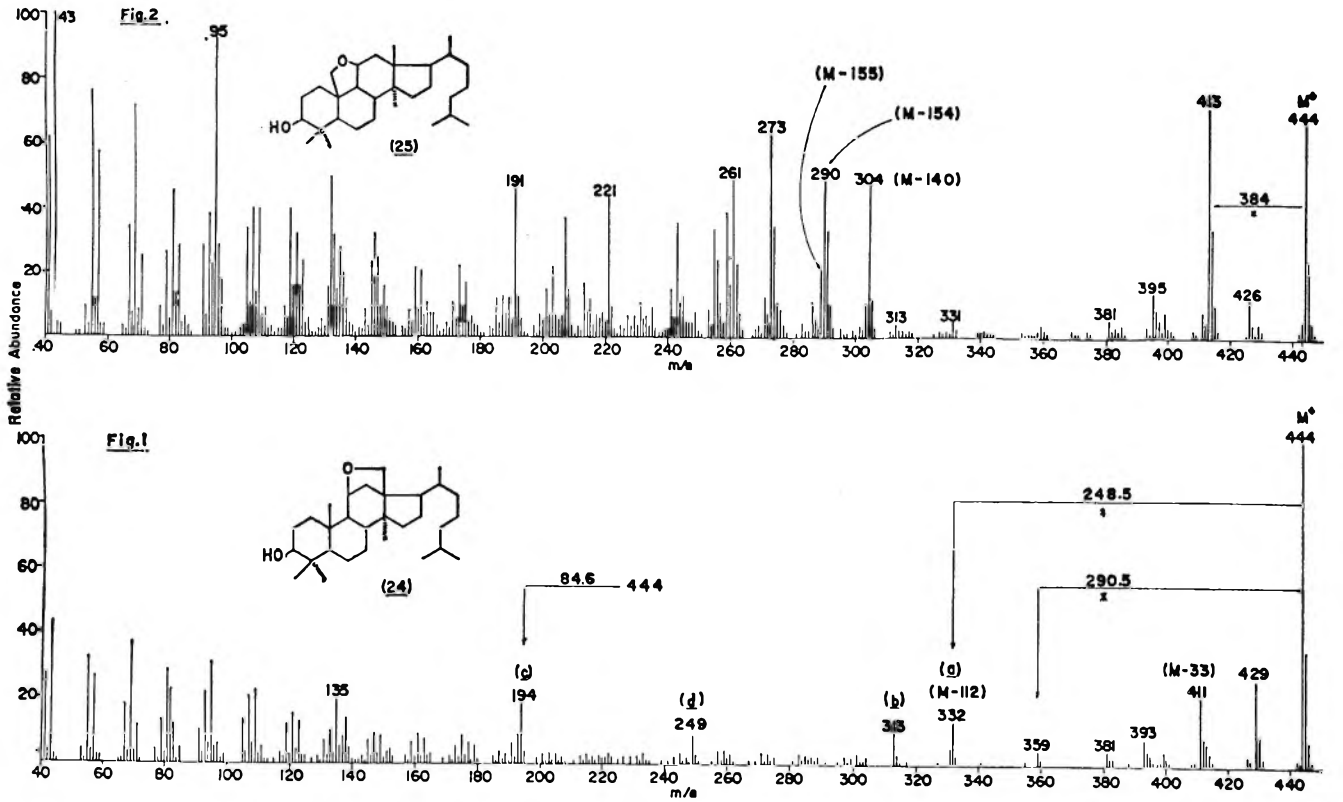
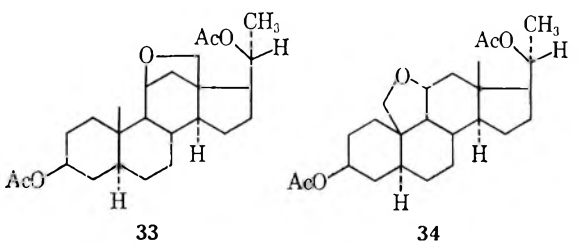


Figure 1.—Mass spectrum of 11β,18-epoxylanostan-3β-ol (24).
Figure 2.—Mass spectrum of 11β,19-epoxylanostan-3β-ol (25).



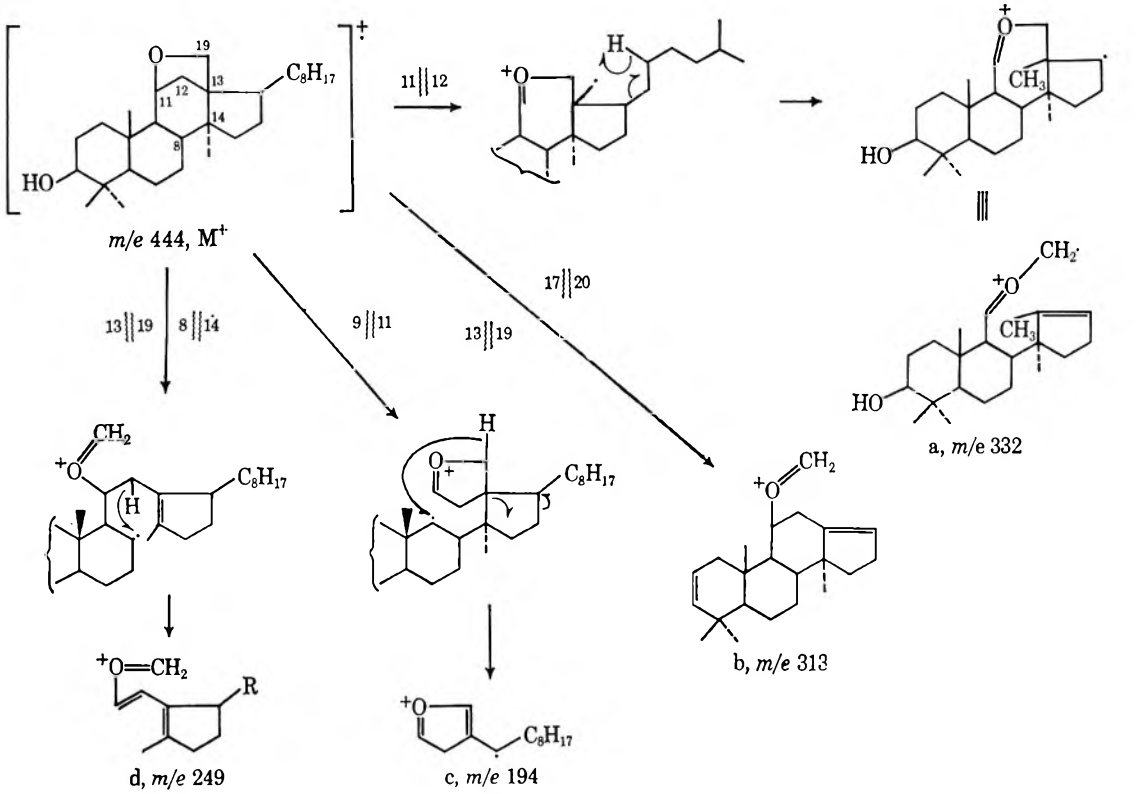
33 34

protons of the 11β,19-ether alcohol **25** and of its acetate **28** appeared each as a pair of doublets centered at 3.82 and 3.64 ppm (J = 8 Hz). In addition, the lower field doublet is further split (J = 1.5 Hz) into doublets probably by coupling with the 4β-methyl protons. In contrast to such spatial dissymmetry in these 11β,19-lanostane ethers, the 19-methylene protons of the steroid analog **34** are reported to be equivalent. It is worthy of note that an almost diagnostic sharp doublet (J = 6 Hz) appears for the 11β,18 ethers **24**, **26**, and **32** and 18,11β-lactone **27** as well as for the steroidal 11β,18 ether **33** and an earlier reported[28] 11β,18-steroidal lactone, centered at 4.27–4.30 ppm for ethers and at 4.80–4.93 ppm for the lactones. Indeed, molecular models show a dihedral angle of 45° between the 11α and 12β protons, and therefore it may be reasonable to assign the observed spin coupling to these protons. The dihedral angle was estimated to be 75 to 83° for proton pairs 11α,9α and 11α,12α on the basis of molecular models, and accordingly no coupling is associated with them. In this connection the 3β-acetoxylanostane-18,11β-lactone (**27**) also shows a one-proton quartet centered at 2.52 ppm ($J_{12\beta,11\alpha}$ = 6 Hz, $J_{12\alpha,12\beta}$ = 12.5 Hz) and assigned to the C-12 (β) equatorial proton. The latter is obviously coupled with the 11α proton in agreement with the above-cited observations. Such a low field quartet (at 2.61 ppm) has been found earlier[29] for the 1β-equatorial proton of a steroidal 19,2β-lactone, and its position was verified by double and triple resonance techniques. The 11α protons in the 11β,19-epoxylanostanes **25** and **28**, as well as in the analogous steroidal ether **34**, appear as multiplets at 4.13 and 4.25 ppm, respectively.

The mass spectra (Figures 1 and 2) of the above lanostane ethers deserve some comment. Interestingly, both the 11β,18-ether alcohol **24** and its acetate **26**, as well as the 3-keto derivative **32**, show the molecular ion as base peak. No significant change was observed in the spectrum of the hydroxy compound at low voltage (12 and 15 eV). All three 11,18-ether derivatives show a loss of 33 mass units, corresponding to the combined loss of methyl and water. A possible diagnostic fragment for the 11β,18 ethers, corresponding to the loss of 112 mass units, could be formulated, for example as fragment a for the 3-hydroxy derivative **24**, resulting from the elimination of the side chain and appropriate metastable peaks were observed for this transition. Such fragmentation is not observed in the case of the 11β,19 ether **25** and its acetate **28**. Also, concomitant elimination of the 3β substituent and loss of the side chain lead to a fragment b (*m/e* 313) found in both the 11β,18-ether alcohol **24** and its acetate **26**, while in the 3-keto compound only the loss of the side chain (M − 113) was observed. One of the possible formulations for a significant fragment (*m/e* 194), common to all the above 11,18 ethers, is depicted by formula c. The loss of one C-18 hydrogen is proposed on the basis of the spectrum of the 18,18-dideuterio derivative. Our proposed mechanism provides for a fully

(29) N. Bhacca, M. E. Wolff, and R. Kwok, *J. Amer. Chem. Soc.*, **84**, 4976 (1962).

SCHEME III



conjugated radical ion and its direct formation from the respective molecular ions of the various derivatives is indicated by the presence of proper metastable ions. Lastly, an ion of mass 249, observed in the spectra of all 11,18 ethers, could be formulated as fragment d, but no further evidence indicates its mode of formation or its structural formulation (Scheme III).

In contrast to the relatively simple mass spectra of the 11,18 ethers, the isomeric 11,19 ethers undergo very extensive fragmentation. Characteristically ring-D fragmentation processes resulting in loss of 155, 154, and 140 mass units are prevalent. Fragmentation modes arising from ring D cleavages have been studied[30] in detail in our laboratory.

To complete our synthetic scheme, the 3β-acetoxylanostane-18,11β-lactone (**27**) was reduced with lithium aluminum hydride to yield lanostane-3β,11β,18-triol (**21**), which proved to be identical with the triol derived from the sea cucumber aglycone seychellogenin (**9**) on the basis of mixture melting point, rotation, and identity of all spectral characteristics.

Although the chemical and spectroscopic properties of the minor lead tetraacetate product, 11β,19-epoxylanostan-3β-ol (**25**), were consistent with its structure, unambiguous chemical proof appeared to be in order. A suitable material was the known[23] 11β,19-cyclolanostane-3β,11α-diol 3-acetate (**23**) whose structure had been proved[23,31] unambiguously by chemical correlation with cycloartenol (**35**). Thus lead tetraacetate oxidation of the cyclobutanol **23** yielded the known[23] 3β,19-dihydroxylanostan-11-one 3-acetate (**36**), which by lithium aluminum hydride reduction gave lanostane-3β,11β,19-triol (**37**). This triol was identical in all respects with the lithium aluminum hydride reduction product of the oxo-acid ester **30**.

In conclusion, the successful interconversion of seychellogenin and lanosterol establishes the complete structure of the marine sapogenin and its stereochemistry at every position but C-20. It is safe to assume, therefore, that all other holothurinogenins with hydroxyl groups at C-17 (**1**,[5,6] **3**,[7] **4**,[8] **5**,[8] **8**,[9]) are also based on a lanostane skeleton.

Experimental Section

Melting points were measured on a Kofler hot-stage microscope and are uncorrected. All rotations were determined using chloroform as solvent. Infrared spectra were obtained using Perkin-Elmer infracord or Model 421 recording spectrophotometers. Ultraviolet spectra were measured in 95% ethanol on a Cary-14 recording spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian T-60, A-60, or HA-100 spectrometer under the supervision of Dr. L. J. Durham. In all cases deuteriochloroform was employed as solvent and tetramethylsilane (δ 0.00 ppm) as internal reference. The visually most intense signal in the methyl region (δ 0.5–1.5) is underlined in the presentation of data. Microanalyses were carried out by Messrs. E. Meier and J. Consul. Mass spectra (70 eV) were obtained by Dr. A. M. Duffield, Mr. R. Ross, and Mr. R. T. Conover with an AEI MS-9 mass spectrometer and in some instances with an Atlas CH-4 mass spectrometer, both equipped with a direct inlet system. Column chromatographies were performed using Davison 60–200 mesh silica gel. Analytical scale thin layer chromatography (tlc) was carried out on 5 × 20 cm, 250-μ silica gel HF plates. Substances were visualized on these plates either by exposure to iodine vapor or by spraying with ceric sulfate solution (2% in 2 *N* sulfuric acid) followed by brief heating on a hot plate. Materials were located on the preparative silica gel plates by iodine vapor or, alternatively, by vertical spotting of ceric sulfate solution, followed by activation of the strip with hot wire from above.

Seychellogenin (**9**).—The isolation, acid hydrolysis of the crude saponins, and the purification of seychellogenin have been described previously.[9,12] Physical properties of seychellogenin: mp (after sublimation) 234–238°; $[\alpha]^{26}D$ −7° (c 1.6); ir ($CHCl_3$)

(30) L. Tökés, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968).

(31) S. Corsano and G. Nicita, *Ric. Sci.*, **37**, 351 (1967).

3300 (OH) and 1755 cm^{-1} (lactone C=O); uv max 237 nm sh (ϵ 11,000), 244 (12,000), and 252 nm sh (8200); nmr δ 0.83 + 0.90 + 0.92 + 1.01 + 1.11 (CH_3-19, -26, -27, -30, -31, -32), 1.40 (CH_3-21), 2.55 (broad d, 2, CH_2-12), 3.23 (m, 1, CH-3), 5.25 and 5.62 (m, 1 each, CH-7 and CH-11); mass spectrum (rel intensity) *m/e* 456 (20, M + 2, probably dihydro contaminant), 454 (100, M^+), 441 (5), 439 (5), 421 (48), 411 (6), 395.33055 (62, $C_{28}H_{43}O$ requires 395.33137), 393 (11), 377.32070 (18, $C_{28}H_{41}$ requires 377.32081), 368.27022 (34, $C_{25}H_{36}O_2$ requires 368.27152), 367.26405 (88, $C_{25}H_{35}O_2$ requires 367.26369), 283 (15), and 43 (100).

Anal. Calcd for $C_{30}H_{46}O_3$: mol wt, 454.34404. Found: mol wt (mass spectrometry), 454.34468.

Seychellogenin 3β-Acetate.—Seychellogenin (9, 100 mg) was acetylated with 1:1 acetic acid–pyridine (6 ml) at room temperature overnight. After the usual work-up seychellogenin 3β-acetate was obtained: mp 214–217° (from acetone–ethanol); $[\alpha]^{24}D$ +21° (c 0.9); ir (KBr) 1763 (lactone C=O), 1736 (ester C=O), 1650 and 1240 cm^{-1}; uv max 237 nm sh (ϵ 11,500), 244 (12,700), and 252 sh (9100); nmr δ 0.83 + 9.91 + 0.95 + 0.98 + 1.01 + 1.13 (CH_3-19, -26, -27, -30, -31, -32), 1.40 (s, 3, CH_3-21), 2.05 (s, 3, $OCOCH_3$), 2.5 (broad d, 2, CH_2-12), 4.5 (m, 1, CH-3), 5.2 and 5.5 (m, 1, each CH-7 and CH-11); mass spectrum *m/e* (rel intensity) 498 (18, M + 2, dihydro impurity), 496 (100, M^+), 481 (3, M − CH_3), 453 [6, M − (CH_3 + H_2O)], 437 [83, M − (CO_2 + CH_3)], 463 (9, M − AcOH), 421 [74, M − (AcOH + CH_3)], 393 (11), 377 [23, M − (CH_3 + CO_2 + AcOH)], 368 (38), 367 (98, ring-A fragmentation), 325 [15, M − (CO_2 + CH_3 + side chain)], and 43 (96).

Anal. Calcd for $C_{32}H_{48}O_4$: C, 77.38; H, 9.74. Found: C, 77.21; H, 9.75.

Lithium Aluminum Hydride Reduction of Seychellogenin (9).—Seychellogenin (130 mg) was reduced with lithium aluminum hydride (200 mg) in tetrahydrofuran (20 ml) at reflux temperature over a period of 4 hr. After work-up with saturated sodium sulfate solution, the triol 11 was crystallized from chloroform–methanol: mp 172–173° (transition at 161–170°); $[\alpha]^{24}D$ +47° (c 0.6); ir ($CHCl_3$) 3620 (sharp), 3390 (broad), and 1050 cm^{-1}; uv max 236, 243, and 252 nm; nmr δ 1.31 + 1.25 + 0.98 + 0.92 + 0.87 + 0.83 (CH_3-19, -21, -26, -27, -30, -31, -32), 3.1–3.5 (m, CH_2-18 and CH-3), 5.4 (m, CH-7 and CH-11); mass spectrum (rel intensity) *m/e* 458 (1, M^+), 440 (10, M − H_2O), 425 [9, M − (H_2O + CH_3)], 422 [19, M − (H_2O + H_2O)], 409 [100, M − (H_2O + CH_2OH)], 407 [19, M − (H_2O + H_2O + CH_3)], and 355 (10, M − C_6H_{13} side chain).

Anal. Calcd for $C_{30}H_{50}O_3$: mol wt, 458. Found: mol wt (mass spectrometry), 458.

Acetylation of the Triol 11.—The triol 11 (140 mg) was acetylated in a 1:1 mixture of pyridine–acetic anhydride (16 ml) at room temperature overnight. After the usual work-up and preparative tlc (silica gel HF, 10% ethyl acetate–benzene, R_f 0.4) the triol diacetate 12 (110 mg) could be crystallized from benzene–hexane (containing a trace of pyridine): mp 139–144°; $[\alpha]^{26}D$ +67° (c 1.3); ir (KBr) 3550 (sharp), 3490 (broad), 1737, 1375, and 1240 cm^{-1}; uv max 235 nm (ϵ 13,400), 243 (15,400), and 252 (10,200); nmr δ 0.83 + 0.88 + 0.92 + 0.95 + 1.02 (18, CH_3-19, -26, -27, -30, -31, -32), 1.32 (s, 3, CH_3-21), 2.02 (s, 6, $OCOCH_3$), AB quartet at 4.20 and 3.79 (1 each, J = 11 Hz, CH_2-18), 4.54 (m, 1, CH-3), 5.2–5.7 (broad, m, 2, CH-7 and CH-11); mass spectrum (rel intensity) *m/e* 542 (1, M^+), 524 (18), 509 [7, M − (H_2O + CH_3)], 482 (7, M − AcOH), 464 [35, M − (H_2O + AcOH)], 451 [70, M − (H_2O + CH_2OAc)], 449 [48, M − (H_2O + AcOH + CH_3)], 411 (20), 407 [14, M − (AcOH + CH_2OAc + H_2O)], 397 [30, M − (AcOH + C_6H_{13})], 389 [20, M − (2AcOH + H_2O + CH_3)], 69 (10), and 43 (235, base peak).

Anal. Calcd for $C_{34}H_{54}O_5$: C, 75.23; H, 10.03. Found: C, 75.30; H, 10.03.

Reduction of seychellogenin (9) with lithium aluminum deuteride followed by acetylation gave the corresponding C_{18}-dideuterio derivative, the spectrum of which exhibited the following peaks: *m/e* 544 (1, M^+), 526 (26), 511 (5), 484 (20), 466 (20), 465 (23), 451 (100), 449 (2), 437 (16), 413 (19), 409 (17), 401 (26), 399 (62), 391 (25), and 43 (183, base peak).

Dehydration of 3β,18-Diacetoxy-20ξ-hydroxylanosta-7,9(11)-diene (12).—The triol diacetate 12 (94 mg) in pyridine (18 ml) was treated with phosphorus oxychloride[15] (3 ml) at room temperature for 1 day. After the excess reagent was destroyed with water, ether extraction gave a mixture of products which were separated on silver nitrate impregnated silica gel HF plates (1.1% ethyl acetate–benzene, developed twice). The less polar isomer, 3β,18-diacetoxylanosta-7,9(11),20(22)-triene (14) (R_f 0.65, 28 mg, 30%), was crystallized from dichloromethane–methanol: mp 120–122°; $[\alpha]^{26}D$ +18° (c 0.9); ir ($CHCl_3$) 1755 and 1255 cm^{-1}; uv max 235 nm (ϵ 11,700), 242 (13,900), and 251 (9000); nmr δ 0.81 + 0.87 + 0.90 + 0.92 + 0.95 + 1.00 (CH_3-19, -26, -27, -30, -31, -32), 1.65 (s, half width = 3 Hz, 3, CH_3-21), 1.88 (s, 3, CH_3OCO-18), 2.03 (s, 3, CH_3OCO-3), AB quartet at 3.76 and 3.50 (1 each, J = 11 Hz, CH_2-18), 4.50 (m, 1, CH-3) 5.15–5.55 (broad m, 3, CH-7, CH-11, and CH-22); mass spectrum (rel intensity) *m/e* 524 (27, M^+), 509 (5, M − CH_3), 464 [52, M − AcOH), 451 (90, M − CH_2OAc), 449 [63, M − (CH_2OAc + AcOH)], 411 (26), 407 (15), 391 (40), 389 (41), 355 (18), 35 (16), 315 (76), 313 (95), 312 (25), 255 (50), 69 (100), and 43 (224, base peak).

Anal. Calcd for $C_{34}H_{52}O_4$: mol wt, 524. Found: mol wt (mass spectrometry), 524.

The more polar olefin, 3β,18-diacetoxylanosta-7,9(11),20(21)-triene (13) (R_f 0.53, 34 mg, 37%), was crystallized from chloroform–methanol: mp 130–131°; $[\alpha]^{25}D$ +28° (c 0.5); ir ($CHCl_3$) 1735, 1650, 893 (C=CH_2), and 1250 cm^{-1} uv max 235 nm (ϵ 12,100), 242 (14,200) and 251 (9300); nmr δ 0.83 + 0.88 + 0.93 + 0.95 + 1.01 (CH_3-19, -26, -27, -30, -31, -32), 1.88 (s, 3, CH_3OCO-18), 2.04 (s, 3, CH_3OCO-3), AB quartet at 3.85 and 3.50 (1 each, J = 11 Hz, CH_2-18), 4.55 (m, 1, CH-3), 4.80 (broad d, 2, J = 5 Hz, CH_2-21), 5.45 (broad m, 2, CH-7 and CH-11); mass spectrum (rel intensity) *m/e* 524 (34, M^+), 509 (7), 464 (61), 451 (90), 449 (68), 411 (53), 407 (16), 391 (36), 389 (47), 379 (15), 355 (22), 351 (18), 315 (31), 313 (61), 312 (35), 255 (37), 69 (100), and 43 (242, base peak).

Anal. Calcd for $C_{34}H_{52}O_4$: mol wt, 524.38654. Found: mol wt (mass spectrometry), 524.38714.

Catalytic Hydrogenation of the $\Delta^{20(21)}$ Olefin 13. The olefin 13 (127 mg) in ethyl acetate (25 ml) was hydrogenated with 120 mg of platinum oxide at room temperature for 4 hr giving the C-20 epimeric mixture 15: mp 97–105°; $[\alpha]^{27}D$ +43° (c 1.2); ir (KBr) 1738 and 1240 cm^{-1}; uv max 235 nm (ϵ 10,500), 242 (12,300), and 251 (8100); nmr δ 0.82 + 0.88 + 0.90 + 0.93 + 0.96 (CH_3-19, -21, -26, -27, -30, -31, -32), 1.98 (s, 3, CH_3OCO-18), 2.04 (s, 3, CH_3OCO-3), 3.75 (broad s, 2, half width = 3 Hz, CH_2-18), 4.5 (m, 1, CH-3), and 5.4 (broad m, ~1.5, CH-7 and CH-11); mass spectrum (rel intensity) *m/e* 528 (12, M′+, dihydro compound], 526 (13, M^+), 468 (12, M′ − AcOH), 466 (46, M − AcOH), 453 (34), 451 (12), 411 (7), 393 [100, M − (AcOH + CH_2OAc)], 391 (27), 353 (38), 297 (38), 257 (65), 171 (39), 145 (40), 69 (64) and 43 (145).

Anal. Calcd for $C_{34}H_{54}O_4$: mol wt, 526. Found: mol wt (mass spectrometry), 526.

Catalytic Hydrogenation of the $\Delta^{20(22)}$ Olefin 14.—Hydrogenation of the olefin 14 (18 mg) in ethyl acetate (15 ml) with 25 ml of platinum oxide at room temperature for 24 hr yielded the diacetate 15 (18 mg), identical with that reported above on the basis of mass spectral, ultraviolet, and thin layer chromatographic comparison.

Chromium Trioxide Oxidation of 3β,18-Diacetoxy-20ξ-lanosta-7,9(11)-diene (15).—The diene 15 (120 mg) in acetic acid (1 ml) was treated with chromium trioxide solution (200 mg, in 1 ml 8:2 acetic acid–water) at 60° over a period of 1 hr. The mixture was allowed to stand at room temperature for a further 2 hr and then poured onto ice (200 ml) and extracted with ether. The product (140 mg) resulting after removal of solvent was purified by tlc (silica gel HF, 5% ethyl acetate–benzene, developed three times). The uv-active fraction (R_f 0.55, 55 mg, 45%) was identified as 3β,18-diacetoxy-20ξ-lanost-8-ene-7,11-dione (16): mp 105–109° (diethyl ether–methanol); $[\alpha]^{27}D$ +82° (c 1.0) ir (KBr) 1736, 1671, and 1240 cm^{-1}; uv max 271 nm (ϵ 7080); nmr δ 0.81 + 0.90 + 0.93 + 1.20 + 1.28 (CH_3-19, -21, -26, -27, -30, -31, -32), 2.03 and 2.00 (s, 3, each, CH_3OCO-3 and -18), coalescing AB quartet at 3.92 and 3.98 (2, CH_2-18) and 4.53 (q, 1, J = 6.5 and 9 Hz, CH-3); mass spectrum (rel intensity) *m/e* 556 (100, M^+), 528 (2), 514 (13), 496 (93, M − AcOH), 481 (14), 468 (9), 436 (10), 384 (14), 383 (13), 287 (20), 187 (22), 121 (20), and 43 (75).

Anal. Calcd for $C_{34}H_{52}O_6$: mol wt, 556. Found: mol wt (mass spectrometry), 556.

Zinc–Acetic Acid Reduction of Ene–Dione 16.—Zinc dust (200 mg) was added to a solution of the ene–dione 16 (53 mg) in refluxing glacial acetic acid (10 ml) over a period of 30 min. After refluxing for 5 hr, the reaction mixture was poured onto ice and extracted with ether. Purification of the product by tlc (silica

gel HF, 5% ethyl acetate–benzene, developed three times) gave a C-20 epimeric mixture of 7,11 diketone **17** (41 mg, 77%) as an amorphic solid: $[\alpha]^{26}D$ +36° (*c* 1.1); ir (KBr) 1735, 1704, and 1240 cm^{-1}; nmr δ 0.82 + 0.85 + 0.92 (CH_3-21, -26, -27, -30, -31), 1.24 and 1.32 (s, 3 each, CH_3-19 and -32), 2.04 (s, 6, CH_3OCO-3 and -18), 4.05 (t, 2, CH-$_2$18), 4.53 (q, 1, *J* = 6.5 and 9 Hz, CH-3); mass spectrum (rel intensity) *m/e* 558 (100, M^+), 516 (4), 498 (10), 485 (10), 483 (11), 456 (25), 455 (7), 423 (15), 385 (5), 357 (5), 303 (5), 275 (7), 251 (5), 219 (7), 207 (6), 191 (14), 121 (23), and 43 (56).

Anal. Calcd for $C_{34}H_{54}O_6$: mol wt, 588. Found: mol wt (mass spectrometry), 558.

Preparation of 7-Ethylene Thioketal 18.—The diketone **17** (40 mg) in ethanedithiol (70 drops) and boron trifluoride–etherate (25 drops) was stirred for 2 hr at room temperature, the mixture diluted with benzene, and washed with aqueous sodium hydroxide solution (4%) followed by saturated sodium chloride solution. Evaporation of the solvent yielded a yellow gum (45 mg), which, on thin layer chromatoplates (silica gel HF, 2% ethyl acetate–benzene, developed twice) indicated very little starting material and two distinct major components with R_f values 0.41 and 0.27 assigned to the C-20 epimeric mixture of 3,18-diacetoxy-20ξ-lanostane-7,11-dione 7-ethylene thioketals (**18**): nmr (on crude mixture in pyridine) δ 0.83 + 0.90 + 0.96 (CH_3-21, -26, -27, -30, 31), 1.26 (s, 3, CH_3-19), 1.50 (s, 3, CH_3-32), 2.02 and 2.08 (s, 3 each, CH_3OCO-3, and -18), 3.27 (s, 4, $-SCH_2CH_2S-$) and 4.2–4.9 (broad m, 3, CH_2-18 and CH-3).

Anal. Calcd for $C_{36}H_{58}O_6S_2$: mol wt 634. Found: mol wt (mass spectrometry), 634.

Raney Nickel Desulfurization of 7-Ethylene Thioketal 18.—Excess Raney nickel[32] was added to a solution (diethyl ether–ethanol, 2:3, 20 ml) of the crude 7-ethylene thioketal **18** (40 mg). After 4-hr refluxing additional Raney nickel was added and refluxing was continued for 24 hr. The reaction mixture was filtered through celite and on evaporation of the solvent, a pale yellow gum resulted (44 mg). Preparative tlc (silica gel HF, 2% ethyl acetate–benzene, developed three times) yielded two well-separated components (R_f 0.44 and 0.29).

The less polar component, 3β,18-diacetoxy-20-epilanostan-11-one (**19**) (R_f 0.44, 10.3 mg, 27%), was crystallized from acetone–hexane: mp 140.5–143°; $[\alpha]^{27}D$ +38° (*c* 1.1); ir (KBr) 1737, 1700, 1240, and 1030 cm^{-1}; nmr δ 0.83 + 0.84 + 0.87 + 0.88 + 1.08 + 1.13 (CH_3-19, -21, -26, -27, -30, -31, -32), 203 (s, 6, CH_3OCO-3 and -18), AB quartet at 2.67 and 2.46 (1 each, *J* = 14 Hz, CH_2-12), broad doublet centered at 2.8 (1, CHβ-1), 4.00 (s, 2, CH_2-18), 4.47 (s, 1, CH-3); mass spectrum (rel intensity) *m/e* 544 (18, M^+), 502 (1), 484 (48), 471 (20), 442 (8), 441 (11), 411 (11), 399 (12), 361 (100), 348 (13), 301 (14), 275 (11), 263 (29), 193 (17), 135 (33), and 43 (69).

Anal. Calcd for $C_{34}H_{56}O_5$: mol wt, 544.41275. Found: mol wt (mass spectrometry), 544.41228.

The more polar component, 3β,18-diacetoxylanostan-11-one (**20**) (R_f 0.29, 13.4 mg, 34%), was crystallized from ether–hexane: mp 130–131°; $[\alpha]^{26}D$ +53° (*c* 1.4); ir (KBr) 1735, 1700, 1240, and 1025 cm^{-1}; nmr δ 0.83 + 0.84 + 0.87 + 0.89 (CH_3-21, -26, -27, -30, -31), 1.08 and 1.13 (s, 3, each, CH_3-32, -19), 2.03 (CH_3OCO-3 and -18) a pair of doublets at 2.45 and 2.65 (d, 1 each, *J* = 14 Hz, CH_2-12), 2.85 (broad d, 1, CHβ-1) 4.02 (broad s, 2, CH_2-18), 4.47 (m, 1, CH-3); mass spectrum (rel intensity) *m/e* 544 (25, M^+), 502 (2), 484 (40), 471 (20), 442 (8), 441 (10), 411 (9), 399 (10), 361 (100), 348 (11), 301 (8), 275 (8), 263 (35), 175 (14), 135 (30), and 43 (53).

Anal. Calcd for $C_{34}H_{56}O_5$: mol wt, 544.41275. Found: mol wt (mass spectrometry), 544.41228.

Lithium Aluminum Hydride Reduction of 3β,18-Diacetoxylanostan-11-one (20).—The 11 ketone **20** was reduced with excess lithium aluminum hydride in tetrahydrofuran (4 ml) at reflux temperature overnight. After work-up with saturated sodium sulfate solution, the triol **21** (14 mg) was obtained: mp 228–229° (after sublimation at 2 × 10^{-5} mm, approx 170°); $[\alpha]^{26}D$ +43° (*c* 1.0); ir 3410 and 1030 cm^{-1}; nmr δ 0.82 + 0.90 + 0.97 (CH_3-21, -26, -27, -30, -31, -32), 1.18 (s, 3, CH_3-19), 3.25 (m, 1, CH-3), 3.7 (m, 2, CH_2-18), 4.26 (m, 1, CH-11); mass spectrum (rel intensity) *m/e* 444 (18, M − H_2O), 429 (20), 414 (37), 413 (15), 411 (26), 399 (18), 395, 393, 381 (10), 301 (88), 283 (21), 220 (23), and 193 (100 base peak).

(32) A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, **68**, 1471 (1946).

Mixture melting point (227–229°), comparison of the physical data, and identical tlc behavior (R_f 0.40, silica gel HF, 4:1 hexane–acetone, developed three times) established its identity with the triol **21** derived from lanosterol.

Lead Tetraacetate–Iodine–Lithium Aluminum Hydride Reaction on 11β-Hydroxylanostan-3β-yl Acetate (22).[33]—Lead tetraacetate (3.0 g), glacial acetic acid (40 ml), and iodine (1.5 g) in cyclohexane (dry) (80 ml), was stirred for 10 min at room temperature. A cyclohexane solution (150 ml) of 11β-hydroxylanostan-3β-yl acetate (**22**)[12] (3.0 g, mp 215–216°) was added and the reaction mixture irradiated and kept at reflux temperature by means of a 500-W tungsten lamp. After 10 hr, additional lead tetraacetate (2.0 g) and iodine (1.0 g) were added, and the addition of lead tetraacetate (2.0 g) was repeated after 10 hr more. In 6 hr the reaction mixture was cooled, diluted with cyclohexane (500 ml), and washed successively with sodium thiosulfate solution (10%, 3 × 100 ml), saturated sodium bicarbonate solution, and saturated sodium chloride solution. Brief drying over anhydrous magnesium sulfate and evaporation of the solvent under reduced pressure yielded a pale yellow gum (4.25 g). This oxidation mixture was reduced with lithium aluminum hydride (5.0 g) in ether (150 ml) at reflux temperature for 10 hr. After work-up with saturated sodium sulfate solution, the amorphous residue (2.70 g) was chromatographed over silica gel [300 g, pretreated with 15% water, eluent hexane–acetone (6:1)]. The initial fractions (1.30 g) contained a mixture of two compounds and the subsequent fractions contained up to 12 components on the basis of analytical tlc (silica gel HF, 4:1 hexane–acetone, developed twice). Preparative tlc (silica gel HF, 9:1 hexane–acetone, four times) on the initial fractions yielded two ethers (R_f 0.42 and 0.30).

(1) 11β,18-Epoxylanostan-3β-ol (**24**) (R_f 0.42, 870 mg, 32%): mp 196–197° (from methanol–chloroform); $[\alpha]^{24}D$ +81° (*c* 1.2); ir (KBr) 3410 and 1020 cm^{-1}; nmr δ 0.73 + 0.82 + 0.86 + 0.88 + 0.95 + 1.02 (CH_3-19, 21, -26, -27, -30, -31, -32), 3.18 (q, 1, *J* = 6.5 and 9 Hz, CH-3), 3.63 (s, 2, CH_2-18), and 4.27 (d, $J_{11\alpha,12\beta}$ = 6 Hz, CH-11); for mass spectrum, see Figure 1.

Anal. Calcd for $C_{30}H_{52}O_2 \cdot {}^1/_2CH_3OH$: C, 79.50; H, 11.81. Found: C, 79.60; H, 11.69.

(2) 11β,19-Epoxylanostan-3β-ol (**25**) (R_f 0.30, 223 mg, 8%): mp 174–175° (from chloroform–methanol); $[\alpha]^{27}D$ +55° (*c* 1.1); ir (KBr) 3440, 1040, and 1010 cm^{-1}; nmr δ 0.61 + 0.68 + 0.81 + 0.86 + 0.91 + 0.91 (CH_3-18, -21, -26, -27, -30, -31, -32), 3.26 (q, 1, *J* = 5.5 and 9 Hz, CH-3), AB quartet at 3.82 and 3.64 (doublet, 1 each, *J* = 8 Hz, 3.82 is pair of narrow doublets, *J* = 1.5 Hz) and 4.13 (m, 1, CH-11); for mass spectrum, see Figure 2.

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 80.85; H, 11.69.

11β,18-Epoxylanostan-3-one (32).—11β,18-Epoxylanostan-3β-ol (**24**) (30 mg) was treated with a pyridine (1 ml) solution of chromium trioxide (30 mg) at room temperature for 5 hr. After the usual work-up, the ketone **32** was crystallized from acetone–methanol: mp 116–117°; $[\alpha]^{24}D$ +78° (*c* 1.4); ir (KBr) 1705 (C=O), 1030, and 1020 cm^{-1}; nmr δ 0.82 + 0.88 + 0.91 + 1.04 (CH_3-21, -26, -27, -30, -31, -32), 1.16 (s, 3, CH_3-19), 3.67 (s, 2, CH_2-18), 4.28 (d, 1, $J_{11\alpha,12\beta}$ = 6 Hz); mass spectrum (rel intensity) *m/e* 442 (84, M^+), 427 (23), 424 (2), 411 (10), 409 (23, 427 → 409, m* 392.5), 397 (7), 357 (7, 442 → 357, m* 288.5), 330 (24, 442 → 330, m* 246.2), 329 (14), 311 (10), 299 (7), 249 (12), 194 (23, 442 → 194, m* 85.2), 193 (14), and 43 (100).

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.30; H, 11.40.

2,2-Dideuterio-11,18-epoxylanostan-3-one.—The ketone **32** (10 mg) was stirred in an aliquot of sodium (100 mg), deuterium oxide (1 ml), and dioxane (2 ml). After 1 day the solvent evaporated under reduced pressure and the exchange repeated with deuterium oxide (1 ml) and dioxane (2 ml) for an additional day. Then the solvent was again evaporated, deuterium oxide (3 ml) was added, and the solution was extracted with chloroform. The product was purified by tlc (silica gel HF, 5% ethyl acetate–benzene, developed twice, R_f 0.4) and crystallized from methanol–chloroform: mp 114–116°; approximate isotopic distribution 1% d_0, 9% d_1, and 90% d_2; mass spectrum (rel intensity) *m/e*

(33) We employed a modification of the procedure of Barton and coworkers (ref 26), who recorded the isolation of 11β,19-epoxylanostan-3β-ol (**25**), mp 177–182°, $[\alpha]D$ +52°, and its 3-acetate (**28**), mp 162–165°, $[\alpha]D$ +61°. Identity of our product was established by direct comparison in Professor Barton's laboratory.

444 (100, M+), 429 (29), 413 (14), 411 (30), 399 (9), 359 (7), 332 (29), 331 (17), 313 (12), 249 (16), 194 (27), 193 (17), and 43 (46).

11β,18-Epoxylanostan-3β-yl Acetate (26).—The 3-hydroxy 11,18 ether **24** was acetylated in 1:1 pyridine–acetic anhydride at room temperature overnight. The product, 11β,18-epoxylanostan-3β-yl acetate (**26**), was crystallized from chloroform–methanol: mp 185.5–186.5°; $[\alpha]^{24}D$ +89° (c 1.2); ir (KBr) 1735, 1240, and 1020 cm^{-1}; nmr δ 0.81 + 0.82 + 0.87 + 0.89 + 10.5 (CH_3-19, -21, -26, -27, -30, -31, -32), 2.02 (s, 3, CH_3-OCO-3), 3.65 (s, 2, CH_2-18), 4.27 (d, 1, $J_{11\alpha,12\beta}$ = 6 Hz, CH-11), 4.5 (m, 1, CH-3); mass spectrum (rel intensity) *m/e* 486 (100, M+), 741 (41), 468 (5), 455 (12), 453 (20, 471 → 453, m* 436), 426 (10), 411 (43, 471 → 411, m* 359), 401 (5, 486 → 401 m* 330), 393 (33, 471 → 393, m* 328), 383 (11), 374 (26, 486 → 374, m* 288), 313 (20), 249 (14), 194 (32, 486 → 194, m* 77.4), 193 (18), and 43 (100).

Anal. Calcd for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 78.73; H, 10.96.

3β-Acetoxylanostane-18,11β-lactone (27).—The ether **26** (200 mg) in acetic acid (1 ml) was treated with chromium trioxide solution (180 mg, in 2 ml of 80% aqueous acetic acid) at room temperature for 5 hr. After the usual work-up, preparative tlc (silica gel HF, 5:1 hexane–acetone) provided the starting material 11β,18-epoxylanostan-3β-yl acetate (**26**) (R_f 0.70, 70 mg), mp 185.5–186.5, and 3β-acetoxylanostane-18,11β-lactone (**27**) (R_f 0.59, 47 mg, 35%): mp 222–222.5° (from chloroform–acetone); $[\alpha]^{24}D$ +73° (c 1.3); ir (KBr) 1762 (five-membered lactone), 1736 (acetate), 1240 and 1030 cm^{-1}; nmr δ 0.79 + 0.83 + 0.85 + 0.87 + 0.89 + 0.93 + 1.03 (CH_3-19, -21, -26, -27, -30, -31, -32), 2.04 (s, 3, CH_3OCO-3), 2.52 (q, 1, *J* = 6 and 12.5 Hz, CH-12β), 4.47 (q, 1, *J* = 6.5 and 9 Hz, CH-3), 4.93 (d, 1, $J_{11\alpha,12\beta}$ = 6 Hz, CH-11); nmr (C_6D_6) δ 0.69 + 0.85 + 0.88 + 0.95 + 0.97 (CH_3-19, -21, -26, -27, -30, -31, -32), 1.75 (s, 3, CH_3OCO-3), 2.27 (q, 1, *J* = 6 and 12.5 Hz, CH-12β), 4.26 (d, 1, $J_{11\alpha,12\beta}$ = 6 Hz, CH-11), 4.58 (q, 1, *J* = 6.5 and 9 Hz, CH-3); mass spectrum (rel intensity) *m/e* 500 (32, M+), 485 (26), 482 (3), 455 (8), 440 (22), 425 (39), 397 (12), 385 (7), 371 (15), 347 (48), 343 (58), 327 (7), 311 (8), 288 (32), 287 (29), 283 (26), 237 (22), 193 (25), 176 (28), 135 (39), and 43 (100).

Anal. Calcd for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.91; H, 10.27.

Lanostane-3β,11β,18-triol (21).—The lactone **27** (35 mg) was reduced with excess lithium aluminum hydride in tetrahydrofuran (3 ml) at room temperature overnight. Work-up with saturated sodium sulfate solution gave lanostane-3β,11β,18-triol (**21**) (32 mg): mp 227–229° (after sublimation at 2 × 10^{-5} mm, *ca.* 170°); $[\alpha]^{27}D$ +43° (c 1.1); ir (KBr) 3410 and 1035 cm^{-1}; nmr δ 0.82 + 0.90 + 0.97 (CH_3-21, -26, -27, -30, -31, -32), 1.18 (s, 3, CH_3-19), 3.25 (m, 1, CH-3), 3.70 (q poor, 2, CH_2-18), 4.26 (m, 1, CH-11), 3.70 + 2.20 + 1.69 (all three singlets exchange in D_2O, HO-3, -11, -18); mass spectrum (rel intensity) *m/e* 444 (11), 429 (9), 414 (43), 413 (13), 411 (10), 399 (16), 395, 393, 381 (6), 301.2537 (85, $C_{21}H_{33}O$ requires 301.2531), 283.2471 (15, $C_{21}H_{31}$ requires 283.2426), 220 (23), and 193.1944 (100, $C_{14}H_{25}$ requires 193.1956).

Anal. Calcd for $C_{30}H_{54}O_3$: C, 77.87; H, 11.76. Found: C, 77.69; H, 11.59.

3β-Acetoxylanostane-18,11β-lactone (**27**) was reduced in a similar manner with lithium aluminum deuteride giving 18,18-dideuteriolanostane-3β,11β,18-triol: mass spectrum (rel intensity) *m/e* 446 (8, M − H_2O), 431 (8), 414 (48), 413 (18), 399 (13), 395 (9), 301 (83), 283 (15), 220 (20), 193 (100, base peak), and 43 (73).

The above 18,18-dideuteriolanostane-3β,11β,18-triol was stirred with *p*-toluenesulfonyl chloride[34] in pyridine at room temperature overnight and the crude product was treated with sodium naphthalide[35] in tetrahydrofuran. Preparative tlc (silica gel HF, 4:1 hexane–acetone, R_f 0.40) gave a small yield of 18,18-dideuterio-11β,18-epoxylanostan-3β-ol: mass spectrum (rel intensity) *m/e* 446 (100 M+), 431 (26), 413 (32), 381 (6), 361 (4), 334 (16), 315 (12), 251 (12), 195 (25), and 193 (12).

11β,19-Epoxylanostan-3β-yl Acetate (28).—The 3β alcohol **25** was acetylated in 1:1 pyridine–acetic anhydride at room temperature overnight. The acetate **28** was crystallized from chloroform–methanol: mp 165–166°; $[\alpha]^{26}D$ +62° (c 1.2); ir (KBr) 1737, 1245, and 1020 cm^{-1}; nmr δ 0.70 + 0.81 + 0.84 + 0.90 (CH_3-18, -21, -26, -27, -30, -31, -32), 2.03 (s, 3, CH_3-OCO-3), AB quartet at 3.65 and 3.83 (1 each, *J* = 8 Hz, CH_2-19), 4.13 (m, 1, CH-11), 4.53 (m, 1, CH-3); mass spectrum (rel intensity) *m/e* 486 (29, M+), 471 (3), 455 (32), 426 (18), 411 (7), 396 (33), 395 (27), 381 (8), 373 (6), 346 (43), 332 (50), 331 (20), 315 (29), 303 (37), 301 (31), 286 (28), 273 (33), 263 (43), 255 (72), 243 (53), 207 (38), 203 (48), 95 (100), and 43 (97).

Anal. Calcd for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 78.86; H, 11.34.

Chromium Trioxide Oxidation of 11β,19-Epoxylanostan-3β-yl Acetate (28).—The ether **28** (35 mg) in acetic acid (1 ml) was treated with chromium trioxide (20 mg in 1 ml of 80% aqueous acetic acid) at room temperature for 4 hr. The excess reagent was decomposed with 2-propanol and the resulting 3β-acetoxy-11-oxolanostan-19-oic acid (**29**) was isolated by preparative tlc (silica gel HF, 4:1 hexane–acetone, developed twice, R_f 0.3, 18 mg): mp 185–188° (from chloroform–acetone); ir ($CHCl_3$) 3540, 2900–3300 (broad), 1730, 1708 (11 ketone), and 1250 cm^{-1}; mass spectrum (rel intensity) *m/e* 516 (5, M+), 498 (7, M − H_2O), 472 (2), 456 (80, M − AcOH), 438 (23, M − (AcOH + H_2O)], 410 [100, M − (AcOH + CO_2H_2)], 395 (10), 393 (16), 377 (7), and 95 (68).

Anal. Calcd for $C_{32}H_{52}O_5$: mol wt, 516. Found: mol wt (mass spectrometry), 516.

The above acid was further characterized by converting it to the methyl ester **30** with diazomethane in ether: mp 140–142° (from ether); $[\alpha]^{25}D$ +74° (c 0.5); ir ($CHCl_3$) 1735–1700 and 1240 cm^{-1}; nmr δ 0.72 + 0.80 + 0.85 + 0.90 + 1.04 (CH_3-18, -21, -26, -27, -30, -31, -32), 2.04 (s, 3, CH_3OCO-3), 3.70 (s, 3, $COOCH_3$-19); mass spectrum (rel intensity) *m/e* 530 (11, M+), 512 (17, M − H_2O), 498 (4), 470 (8, M − AcOH), 456 [60, M − (CO_2Me + CH_3)], 438 (20), 410 (64), 393 (89), 392 (28), 377 (8), and 303 (12).

Anal. Calcd for $C_{33}H_{54}O_5$: mol wt, 530.397. Found: mol wt (mass spectrometry), 530.392.

Lithium Aluminum Hydride Reduction of 3β-Acetoxy-11-oxolanostane-19-carboxylic Acid Methyl Ester 30.—The ester **30** (25 mg) was reduced with lithium aluminum hydride in tetrahydrofuran at reflux temperature for 5 hr. After the usual work-up with saturated sodium sulfate solution, preparative tlc (silica gel HF, 4:1 hexane–acetone, three times) gave lanostane-3β,11β,-19-triol (**37**) (15 mg, R_f 0.23): mp 237–238°; $[\alpha]^{25}D$ +41° (c 0.9); ir (KBr) 3390 and 1030 cm^{-1}. Mixture melting point determination (mp 237–238°) and comparison of its specific rotation and ir spectrum, as well as its identical tlc behavior (in the above system), confirmed its identity with lanostane-3β,11β,-19-triol (**37**) characterized below.

Lanostane-3β,11β,19-triol (37).—3β-Acetoxy-lanostan-19-ol-11-one[23] (**36**) (53 mg, mp 163–165°; $[\alpha]^{26}D$ +54°; lit.[23] mp 157–158°, $[\alpha]D$ +53°, nmr identical) was reduced with lithium aluminum hydride in tetrahydrofuran (4 ml). After the usual work-up and purification (same as above) lanostane-3β,11β,19-triol (**37**) (21 mg) was isolated: mp 237–239° (from chloroform–methanol); $[\alpha]^{25}n$ +43° (c 0.5); ir (KBr) 3390 and 1030 cm^{-1}; nmr 0.79 + 0.91 + 1.00 + 1.02 (CH_3-18, -21, -26, -27, -30, -31, -32), 3.27 (broad m, 1, CH-3), 3,82 (s, 2, CH_2-19), 4.20 (narrow m, 1, CH-11); mass spectrum spectrum (rel intensity) *m/e* 462 (1, M+), 444 (17), 426 (55), 414 (100), 413 (48), 411 (20), 399 (64), 396 (32), 395 (22), 381 (26), 353 (7), and 239 (10).

Anal. Calcd for $C_{30}H_{54}O_3 \cdot {}^1/_2CH_3OH$: C. 76.51; H, 11.79. Found: C, 76.61; H, 11.80.

Registry No.—**9**, 24041-68-7; **9** 3β-acetate, 24041-70-1; **11**, 25116-58-9; **12**, 25116-59-0; **13**, 24041-73-4; **14**, 25116-61-4; **15**, C-20 (*R*), 24041-75-6; **15**, C-20 (*S*), 24041-74-5; **16**, C-20 (*R*), 24041-81-4; **16**, C-20 (*S*), 24041-76-7; **17**, C-20 (*R*), 25116-64-7; **17**, C-20 (*S*), 25158-18-3; **18**, C-20 (*R*), 25158-19-4; **18**, C-20 (*S*), 25158-20-7; **19**, 24041-77-8; **20**, 24041-78-9; **21**, 24041-79-0; **24**, 25116-67-0; **25**, 22417-94-3; **26**, 25116-68-1; **27**, 24041-80-3; **28**, 22417-93-2; **29**, 25116-71-6; **30**, 25116-72-7; **32**, 25116-73-8; **32** (2,2-dideuterio), 25116-74-9; **37**, 25116-75-0.

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A Novel Dehydration Reaction of Steroidal Alcohols

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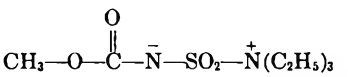
Various steroidal secondary and tertiary alcohols were treated with methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt (**1**), to afford olefins. In most cases, the nature of the alcohol group (secondary, tertiary, homoallylic), its configuration, and the environment are the primary factors governing the course of the reaction. While tertiary alcohols seem to react under milder conditions, they are also subject to rearrangements. The compatibility of a saturated ketone, α,β-unsaturated ketone, aromatic ring, triple bond, acetate, and bismethylenedioxy function with the reagent and the mild reaction conditions (low temperature, neutral medium), the satisfactory yields which were often obtained, as well as the unexpected nature of some products, make it an attractive technique for introduction of double bonds into the steroid molecule.

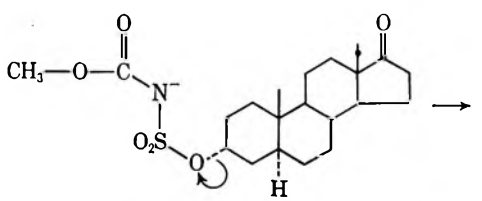
Recently, Burgess, *et al.*,[2] reported the preparation of methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt (**1**) and showed[3] **1** to be a useful reagent for the dehydration of simple alcohols. The authors have also shown that the reaction is at least for secondary alcohols a stereospecific *cis* elimination of first order, which proceeds *via* an ion-pair mechanism and follows Saytzeff's rule.[3]

We wish to report the application of this elimination reaction to secondary and tertiary steroidal alcohols. It is shown that the inner salt **1** is a useful dehydration agent which gives rise to a variety of olefins whose yield and structure depend essentially on the nature of the starting steroidal alcohols.

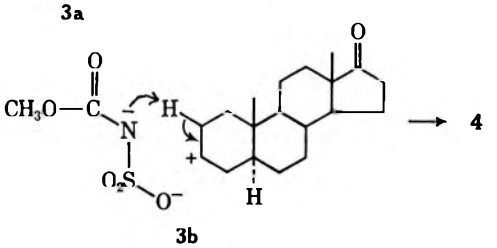


1

The course of the reaction of 3α-hydroxy-5α-androstan-17-one (**2**) with the N-sulfonylamine inner salt **1**, in anhydrous benzene solution at room temperature, was followed by thin layer chromatography (tlc). When there was no alcohol **2** left but only a more polar product, the solution was neutralized and extracted, yielding a compound presumed to be the ester **3a** which decomposed on heating at 90° *in vacuo* by a



3a



3b

cyclic intramolecular hydrogen transfer (see **3b**). Besides sulfur trioxide and methyl carbamate (NH_2COOCH_3), 75% 5α-androst-2-en-17-one (**4**) was obtained (see Table I).

Similarly, 3β-hydroxy-5α-androstan-17-one (**5**) and cholestanol **6** afforded the Δ^2 steroids **4** and **7** in 52 and 63% yield, respectively. The reasonable yield obtained in these dehydrations indicates that the 17-keto group is compatible with the elimination reaction of **2** and **5**. Moreover, no Δ^3 steroid could be isolated at the end of the reaction.

The alcohol group in cholesterol **8** proved to be less amenable to dehydration under the above conditions, since 40% of starting material **8** was recovered along with a 27% yield of cholesta-3,5-diene (**9**) (Table I). The $\Delta^{2,5}$-diene, which may have been formed, could conceivably have rearranged to the isomeric $\Delta^{3,5}$-diene (**9**) during the isolation procedure.

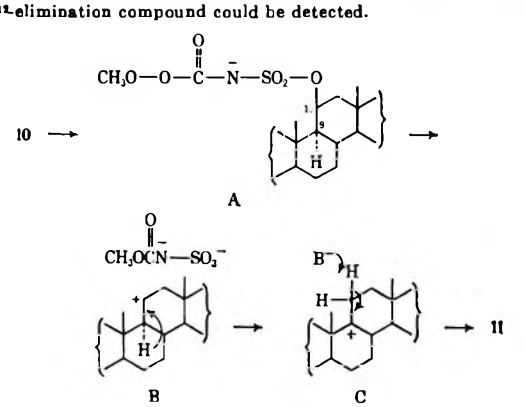
When the elimination reaction was performed with 11β,17α,21-trihydroxy-17:20,20:21-bismethylenedioxypregn-4-ene-3,20-dione (**10**), the $\Delta^{9(11)}$-pregnene (**11**) was formed in 96% yield. This is remarkable because it shows that there is no competing reaction between the inner salt **1** and either the conjugated Δ^4-3 ketone or the bismethylenedioxy grouping.

The $\Delta^{9(11)}$ steroid **11** results presumably from intramolecular hydrogen transfer of the hydrogen atom at C-9 to a cation formed at C-11, followed by proton extraction.[4]

The formation of the $\Delta^{9(11)}$ steroid **11** in high yield is particularly important because of the potential use of this reaction for further introduction of substituents at C-9 and C-11, known to increase the biological activity, *e.g.*, in the corticoid series.

In contrast to the 11β-hydroxy compound **10**, reaction of 11α-hydroxypregn-4-ene-3,20-dione (**12**) with **1** only afforded 9% $\Delta^{9(11)}$-pregnene (**13**). It may be that steric factors make the course of the elimination

(4) The suggested mechanism **10** → A → B → C → **11** also explains why no $\Delta^{11,12}$-elimination compound could be detected.



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(2) G. M. Atkins, Jr., and A. M. Burgess, *J. Amer. Chem. Soc.*, **90**, 4744 (1968).

(3) E. M. Burgess, E. A. Taylor, and H. P. Penton, Jr., 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, Abstracts, No. ORGN-105.

TABLE I

PRODUCTS AND YIELDS OF COMPOUNDS FORMED BY DEHYDRATION OF STEROIDAL ALCOHOLS

Steroidal alcohols	Steroidal olefins formed	Yields, %
3α-Hydroxy-5α-androstan-17-one (2)	5α-Androst-2-en-17-one (4)	75
3β-Hydroxy-5α-androstan-17-one (5)	5α-Androst-2-en-17-one (4)	52
3β-Hydroxy-5α-cholestane (6)	5α-Cholest-2-ene (7)	63
3β-Hydroxy-cholest-5-ene (8)	Cholesta-3,5-diene (9)	27
11β,17α,21-Trihydroxy-17:20,20:21-bismethylenedioxypregn-4-ene-3,20-dione (10)	17α,21-Dihydroxy-17:20,20:21-bismethylenedioxy-pregna-4,9(11)-diene-3,20-dione (11)	96
11α-Hydroxypregn-4-ene-3,20-dione (12)	Pregna-4,9(11)-diene-3,20-dione (13)	9
	17α-Pregna-4,9(11)-diene-3,20-dione (14)	2
3β,17β-Dihydroxy-3α-ethynyl-5α-androstane 17-acetate (15)	3-Ethynyl-17β-hydroxy-5α-androst-2-ene acetate (16)	25
3,17β-Dihydroxy-17α-ethynylestra-1,3,5(10)-triene 3-methyl ether (17)	3-Hydroxy-17-ethynylestra-1,3,5(10),16-tetraene 3-methyl ether (18)	61
	3-Hydroxy-17α-ethynyl-17β-methyl-18-norestra-1,3,5(10),13-tetraene 3-methyl ether (19)	11
2α,17α-Dimethyl-17β-hydroxy-5α-androstan-3-one (20)	2-Methyl-7-methylene-5α-androstan-3-one (21)	74
	2α,17,17-Trimethyl-18-nor-5α-androst-13-en-3-one (22)	10

reaction different in the case of 11α and 11β alcohols **10** and **12**. In any event, the dramatic difference in yields of **11** and **13** is surprising, since the formation of an intermediary 11β ester[4] of **10** should be subjected to more steric hindrance by the 18- and 19-methyl groups, as well as the bismethylenedioxy grouping than in the case of the 11α-hydroxypregnene (**12**).

Worth noting also is the formation of 2% 17α-pregna-4,9(11)-diene-3,20-dione (**14**) during this reaction. The 17α configuration of the methyl ketone is based on the chemical shift of the C-18 methyl resonance (Table II).[5,6]

Attempts to dehydrate some secondary 17β-hydroxy steroids led to a complex mixture of substances which could not be separated and in which no compound was observed in yields exceeding 10%.

Steroidal tertiary alcohols were also submitted to treatment with the N-sulfonylamine inner salt **1**. Reaction of the steroidal alcohols, **15**, **17**, and **20**, with **1** in anhydrous benzene at room temperature was followed by tlc. In these cases, only less polar products were formed. The organic solution was washed with water, dried, and concentrated under reduced pressure to afford *directly* the elimination compounds. No sulfonyl esters were detected which seems to indicate that they are decomposed *in situ* at room temperature.

Under these reaction conditions, 3β,17β-dihydroxy-3α-ethynyl-5α-androstane 17-acetate (**15**) provided 25% Δ^2-androstene **16**, besides 50% of recovered starting material **15**.

Dehydration of 3,17β-dihydroxy-17α-ethynylestra-1,3,5(10)-triene 3-methyl ether (**17**) under the same reaction conditions provided as major product the Δ^{16}-elimination compound **18** (61%), along with 3-hydroxy-17α-ethynyl-17β-methyl-18-norestra-1,3,5-(10),13-tetraene 3-methyl ether (**19**) (11%) which could be separated by tlc. Similarly, 2α,17α-dimethyl-17β-hydroxy-5α-androstan-3-one (**20**) afforded the $\Delta^{17(20)}$-elimination product **21** (74% yield) and the rearranged 17,17-dimethyl compound **22** (10%) (see Table I). The rearranged products, **19** and **22**, presumably result from methyl migration after formation of a carbonium ion at C-17.

It is of interest to note that in the case of dehydration of compounds **15** and **17** the inner salt **1** does not seem to have reacted either with the ethynyl group, or the acetate of **15**, or the aromatic ring of **17**. This emphasizes the applicability of the elimination reaction to numerous polyfunctional molecules. Worth noting also is the good yield in which the methylene compound **21** was formed. In the present case, Saytzeff's rule was not followed. In any event, this constitutes a new method of introducing an *exo*-methylene group at C-17 with potential use in the elaboration of the pregnane and corticoid side chains.

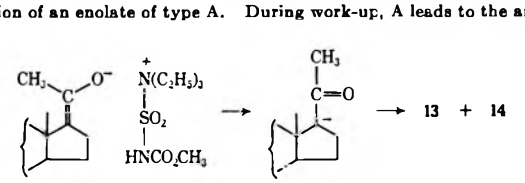
Experimental Section[7]

The physical properties and appropriate references of steroidal olefins are listed in Table II.

Typical Procedure. Reaction of the Secondary Alcohol 2 with the Inner Salt 1.—To a solution of 1 g of **2** in 50 ml of anhydrous benzene, 6.5 g of salt **1**[2] was slowly added. The mixture was stirred for 2 hr at room temperature, the reaction

(5) A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, **86**, 1221 (1964); (b) J. Romo, L. Rodriguez-Hahn, P. Joseph-Nathan, M. Martinez, and P. Crabbé, *Bull. Soc. Chim. Fr.*, 1276 (1964); (c) X. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(6) The partial inversion of configuration at C-17 is attributed to the formation of an enolate of type A. During work-up, A leads to the anion B



A

which gets protonated at C-17 from both sides. A recent experiment has shown that dehydration of 11β-hydroxypregn-4-ene-3,20-dione with the same reagent gives an identical mixture of **13** (four parts) and **14** (one part).

(7) Microanalyses were done by Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany. Melting points were determined in capillary tubes with a Mel-Temp apparatus; they are corrected. Optical rotations were taken between 16 and 22° with a 1-dm tube at sodium D light in chloroform solution. Infrared spectra were taken with a Perkin-Elmer Model 21, NaCl prism. Ultraviolet absorption spectra were obtained with a Beckman spectrophotometer, Model DU, in ethanol solution. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer, for 5–8% (w/v) solutions in deuteriochloroform containing tetramethylsilane (TMS) as internal reference. Resonance frequencies are quoted as parts per million downfield from TMS. Coupling constants are accurate to ±0.5 Hz.

TABLE II

PHYSICAL PROPERTIES OF STEROIDAL OLEFINS

Steroidal olefins	Mp, °C	[α]D, deg	Uv λmax (nm)	Uv ε	Nmr, ppm	Ref
5α-Androst-2-en-17-one (4)	105–106	+136			0.77 (18 H), 0.87 (19 H), 5.6 (2 H, 3 H)	*a*
5α-Cholest-2-ene (7)	73–74	+68			5.6 (2 H, 3 H)	*b*
Cholesta-3,5-diene (9)	77–78	−110	236	7,940	5.65 (m, 3 H, 4 H, 6 H)	*c*
17α,21-Dihydroxy-17:20,20:21-bismethylenedioxypregna-4,9(11)-diene-3,20-dione (11)	222–223	−21	240	16,600	0.8 (18 H), 1.33 (19 H), 3.96 (21 H), 4.66, 5.06, 5.2, 5.56 (BMD), 5.5 (t, J = 3 Hz, 11 H), 5.73 (4 H)	*d*
Pregna-4,9(11)-diene-3,20-dione (13)	118–119	+143 (acetone)	240	15,900	0.67 (18 H), 1.4 (19 H), 2.17 (21 H), 5.56 (t, J = 3 Hz, 11 H), 5.75 (4 H)	*e*
17α-Pregna-4,9(11)-diene-3,20-dione (14)	175–176	±0	238	14,000	0.90 (18 H), 1.31 (19 H), 2.12 (21 H), 5.61 (t, J = 2 Hz, 11 H), 5.76 (4 H)	*f*
3-Ethynyl-17β-hydroxy-5α-androst-2-ene acetate (16)	93–94	+62	224	12,600	0.80 (18 H), 0.81 (19 H), 2.03 (OAc), 2.8 (acetylenic H), 6.0 (d, J = 12 Hz, 2 H)	*g*
3-Hydroxy-17-ethynylestra-1,3,5-(10),16-tetraene 3-methyl ether (18)	153–154	+66	226 278 287	17,400 1,820 1,700	0.82 (18 H), 2.98 (21-acetylenic H), 3.67 (O-CH_3), 6.05 (16 H), 6.8 (m, aromatic H)	*h*
3-Hydroxy-17α-ethynyl-17β-methyl 18-norestra-1,3,5(10),13-tetraene 3-methyl ether (19)	108–109	±0	278 287	2,040 1,860	1.29 (17 Me), 2.14 (21-acetylenic H), 3.72 (O-CH_3), 6.91 (m, aromatic H)	*i*
2α-Methyl-17-methylene-5α-androstan-3-one (21)	142–143	+45			0.8 (18 H), 1.03 (d, J = 4 Hz, 2 Me), 1.09 (19 H), 4.63 (d, J = 2 Hz, C = CH_2)	
2α,17,17-Trimethyl-18-nor-5α-androst-13-en-3-one (22)	129–130	±0			0.97 (17-*gem*-di-Me), 1.05 (d, J = 3 Hz, 2 Me), 1.09 (19 H)	

[a] Reference 8. [b] A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **28**, 275 (1949). [c] J. C. Eck, R. L. van Peursem, and E. W. Hollingsworth, *J. Amer. Chem. Soc.*, **61**, 171 (1939); F. S. Spring and G. Swain, *J. Chem. Soc.*, 83 (1941). [d] L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964). [e] G. Rosenkranz, O. Mancera, and P. Sondheimer, *J. Amer. Chem. Soc.*, **76**, 2227 (1954); H. Reimann, E. P. Oliveto, R. Neri, M. Eisler, and P. Perlman, *ibid.*, **82**, 2308 (1960). [f] *Anal.* Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.65; H, 8.90. Mass spectrum: *m/e* 312 (M^+), 297 ($M - CH_3$). [g] Unpublished result from L. H. Knox, R. Grezemkovsky, and P. Crabbé, (Syntex, S.A.): mp 93–94°; [α]D + 62°; λmax 224 nm (ε 13,200); νmax 1730 cm^{-1}. *Anal.* Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.74; H, 9.33. [h] P. Crabbé, P. Anderson, and E. Verlarde, *J. Amer. Chem. Soc.*, **90**, 2998 (1968). [i] Unpublished result from E. Velarde and P. Crabbé, (Syntex, S.A.): mp 108–109°; [α]D ±0°; λmax 278, 287 nm (ε 2000, 1900). *Anal.* Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 85.63; H, 8.46.

being followed by tlc. The benzene solution was washed with 5% hydrogen chloride and then with water. After distillation of the solvent, the amorphous material obtained was heated under reduced pressure at 90° for 2 hr giving 1 g of product which was chromatographed over Florisil. Elution with hexane–ether (95:5) afforded 680 mg of crystalline **4** (mp 100–104°) (see Table II).[8]

Typical Procedure. Dehydration of the Tertiary Alcohol 20 with the Inner Salt 1.—To a solution of 1 g of **20** in 20 ml of anhydrous benzene, 2.7 g of salt **1**[2] was added. The reaction mixture was stirred at room temperature for 2 hr. The benzene solution was washed with water until neutral, then dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crystalline product was chromatographed over Florisil.

Elution with hexane–ether (96:4) provided 100 mg of the 18-nor steroid **22** (mp 127–128°), which was purified by recrystallization from methanol to afford the analytical sample: mp 129–130°; [α]D ±0°; νmax 1710, 1445 cm^{-1} (see Table II).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.80; H, 10.65.

Further elution with hexane–ether (95:5) afforded 700 mg of crystalline **21** (mp 134–135°) of which the analytical sample was prepared by recrystallization from methanol: mp 142–143°; [α]D +45°; νmax 1710, 1660, 885 cm^{-1} (see Table II); *m/e* 300 (M^+), 285 ($M^+ - CH_3$).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73; O, 5.32. Found: C, 84.12; H, 10.68; O, 5.30.

Registry No.—**4**, 963-75-7; **7**, 570-73-0; **9**, 747-90-0; **11**, 4777-89-3; **13**, 17652-16-3; **14**, 24742-95-8; **16**, 24799-53-9; **18**, 23640-47-3; **19**, 24742-97-0; **21**, 24742-98-1; **22**, 1971-61-5.

Acknowledgment.—We express our sincere gratitude to Dr. E. M. Burgess, Georgia Institute of Technology, for informing us of his observations and results prior to publication and for providing us with the carbethoxysulfamoyl chloride. We thank Syntex, S.A., for a generous gift of steroids, Dr. A. Guzmán, Dr. P. Ortiz de Montellano, and Miss E. Velarde for helpful suggestions.

(8) (a) R. E. Marker, O. Kamm, D. M. Jones, and L. W. Mixon, *J. Amer. Chem. Soc.*, **59**, 1363 (1937); (b) J. Iriarte, G. Rosenkranz, and F. Sondheimer, *J. Org. Chem.*, **20**, 542 (1955); (c) V. Prelog, L. Ruzicka, P. Meister, and P. Wieland, *Helv. Chim. Acta*, **28**, 618 (1945).

Stereoselective Total Synthesis of (±)-Eremoligenol, (±)-Eremophilene, (±)-Valerianol, and (±)-Valencene[1]

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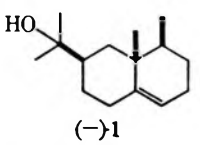
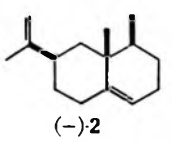
Received January 23, 1970

Synthetic access to the two stereoisomeric classes of bicyclic eremophilone-type sesquiterpenes has been gained through the lithium–ammonia reduction of the methoxymethyl enol ether of ethyl 8β,8aβ-dimethyl-1-oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (**5**). This reaction affords directly the less stable axial ester (**11**), ethyl 8β,8aβ-dimethyl-1,2,3,4,6,7,8,8a-octahydro-2β-naphthoate, which was converted into (±)-eremoligenol and (±)-eremophilene. (±)-Valerianol and (±)-valencene were obtained from the epimeric equatorial ester (**12**).

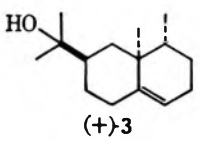
In recent years the number of naturally occurring sesquiterpenoids having the nonisoprenoid decalin nucleus of eremophilone has grown from a few rare examples to a major group of natural products.[3] Among the bicarbocyclic members of this group, there exist two major subclasses which are distinguished by the relative stereochemistry between the C-7 substituent and the *cis* vicinal methyl groups. The biogenetically simplest members with a *cis* relationship between each of the three nuclear substituents are eremoligenol **1**[4] and eremophilene **2**.[5] In the *trans* series the structures **3** and **4** correspond to the natural sesquiterpenes valerianol **3**[6,7] and valencene **4**.[8]



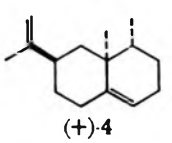
(−)-1



(−)-2

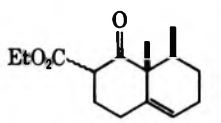


(+)-3

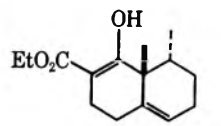


(+)-4

In a previous investigation[9] we have described a synthesis of the bicyclic β-keto esters, **5** and **6**. The former substance, having the annular methyl groups in a *cis* orientation, appeared to offer a simple synthetic entry into either or both of these two stereoisomeric classes of sesquiterpenes. The principal obstacle to this approach was the conversion of the relatively hindered ketone group in the β-keto ester **5** to a methylene group. In this paper we describe a new and direct method for effecting this reductive transformation which has enabled the stereoselective total synthesis of the four sesquiterpenoids **1**–**4** in racemic form.[10,11]



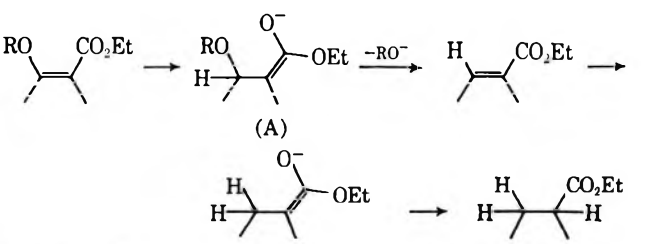
5



6

Although there are a number of different chemical procedures available for the reduction of a ketone carbonyl to a methylene group, the proximity of the ester function in a β-keto ester can present serious complications. The harsh alkaline conditions of the Wolff–Kishner reduction would very likely lead to either (or both) hydrolysis of the ester group[12] and decarboxylation or "acid" cleavage products.[13] The Clemmensen method[14] was not suitable to present case for fear of acid-catalyzed rearrangement or double-bond migration. Although the hydrogenolysis of the dithio ethylene ketal has been used successfully for the reduction of β-keto esters,[15] this approach is not feasible with **5** because the sterically hindered environment of the ketone precludes ketal formation.[9a,c]

With the knowledge that α,β-unsaturated acids may be reduced to saturated acids by means of metal–ammonia solutions,[16] we considered that an enol derivative of a β-keto ester might undergo a double reduction to a saturated ester under these conditions. That is, the enolate anion intermediate (A) in such a reduction should eliminate the enol oxygen to form the α,β-unsaturated ester. The latter would be subject to a second reduction leading to the saturated ester upon quenching of the reaction with a proton donor.



(1) Taken in part from Ph.D. Thesis of J. E. Shaw.

(2) National Science Foundation Trainee, 1965–1969.

(3) For recent reviews see A. R. Pinder, *Perfum. Essent. Oil Rec.*, **59**, 280, 645 (1968).

(4) H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc., C*, 1545 (1966).

(5) J. Křepinský, O. Motl, L. Dolejš, L. Novotný, V. Herout, and R. B. Bates, *Tetrahedron Lett.*, 3315 (1968); J. Hochmannová and V. Herout, *Collect. Czech. Chem. Commun.*, **29**, 2369 (1964); E. Piers and R. J. Keziere, *Tetrahedron Lett.*, 583 (1968).

(6) G. Jommi, J. Křepinský, V. Herout, and F. Sörm, *Collect. Czech. Chem. Commun.*, **34**, 593 (1969).

(7) Also referred to as kusunol: H. Hikino, N. Suzuki, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 832 (1968).

(8) (a) G. L. K. Hunter and W. B. Brogden, *J. Food Sci.*, **30**, (1965); (b) W. D. MacLeod, Jr., *Tetrahedron Lett.*, 4779 (1965).

(9) (a) R. M. Coates and J. E. Shaw, *Chem. Commun.* 47 (1968); (b) *ibid.*, 515 (1968); (c) *J. Amer. Chem. Soc.*, accepted for publication.

(10) A part of this research has appeared as a preliminary communication: R. M. Coates and J. E. Shaw, *Tetrahedron Lett.*, 5405 (1968).

(11) The recently announced synthesis of nootkatone [M. Pesaro, G. Bozzato, and P. Schudel, *Chem. Commun.*, 1152 (1968)], constitutes a total synthesis of (±)-valencene since natural nootkatone has been converted into valencene.[8b] See also J. A. Marshall and R. A. Ruden, *Tetrahedron Lett.*, 1239 (1970).

(12) *Cf.* D. Todd, *Org. React.*, **4**, 378 (1948).

(13) The "acid" cleavage of β-diketones under Wolff–Kishner conditions has been reported: H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 290, 1061 (1952); **86**, 693 (1953); H. Stetter and E. Klauke, *ibid.*, **86**, 513 (1953).

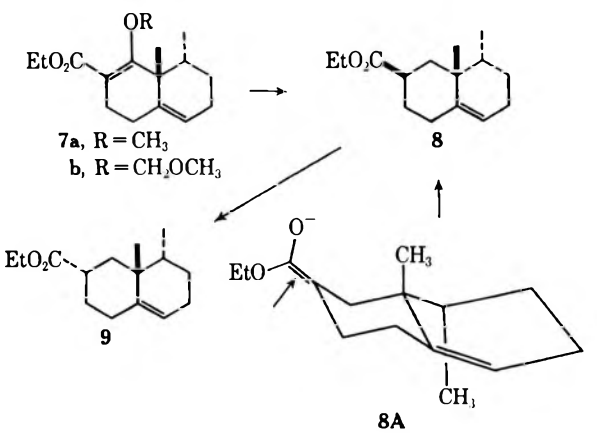
(14) A. Afonso, *J. Amer. Chem. Soc.*, **90**, 7375 (1968).

(15) (a) G. Stork and J. W. Schulenberg, *ibid.*, **84**, 284 (1962); (b) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); (c) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3095 (1968).

(16) G. E. Arth, G. J. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer, and L. H. Sarett, *J. Amer. Chem. Soc.*, **76**, 1715 (1954); F. Sondheimer, W. McCrae, and W. G. Salmond, *ibid.*, **91**, 1228 (1969).

The conversion of 3-ethoxy-2-cyclohexenone to cyclohexanone with lithium in liquid ammonia[17] provides recent precedent for this sequence of reactions with an enol ether of a β diketone.[18] The Birch reduction of trimethylgallic acid to 3,5-dimethoxy-1,4-dihydrobenzoic acid must also involve elimination of alkoxide.[19]

The reaction was first tested with the methyl enol ether **7a**, previously prepared from **6** by treatment with diazomethane.[9b,c] Addition of **7** in ether solution to a 50% excess (*i.e.*, 6 equiv) of lithium in liquid ammonia afforded the octalin ester **8** in 67% yield after quenching with ammonium chloride. That the carbethoxy group of **8** is *cis* (axial) to the quaternary methyl group was established by sodium ethoxide catalyzed equilibration to a more stable isomer **9** (equatorial). This conclusion is confirmed by the difference in the chemical shift for the angular methyl group in the nmr spectra of **8** (τ 9.01) and **9** (τ 8.87). The downfield shift is consistent with literature data for similar pairs of axial and equatorial esters.[15b,20] The formation of the less stable axial isomer **8** is presumably the result of a kinetically controlled protonation of the ester enolate anion (**8A**) from the less hindered equatorial direction.[21]

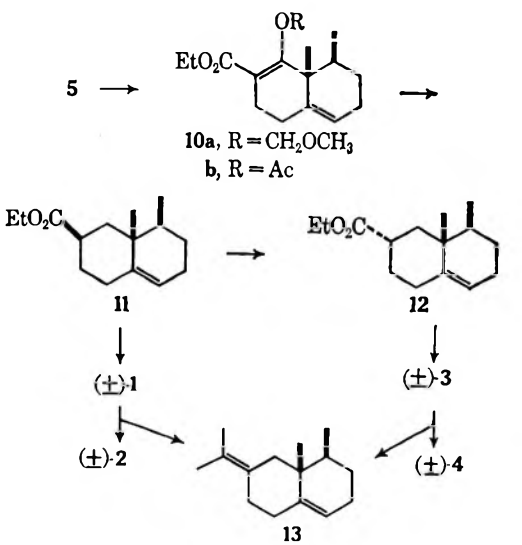


The application of this reduction method to the β-keto ester **5** having the natural *cis* stereochemistry required first conversion to an enol ether derivative. Since methylation with diazomethane proved to be impractically slow, we turn to alkylation of the enolate anion. Although alkylation in dipolar aprotic solvents has been found to give increased proportions of O-alkylation from the ambident enolate anion of β-keto esters,[22] even under optimum conditions the usual alkylating reagents afford considerable quantities of C-alkylation as well. However, Simonsen and Storey have reported that the sodium salt of ethyl acetoacetate reacts with chloromethyl methyl ether to yield only the O-alkylated product.[23] We decided, therefore, to examine the alkylation of the enolate anion of **5** with chloromethyl methyl ether. Hexamethylphosphoramide was selected as solvent since this medium has been found to give high percentages of O-alkylation.[22c-f]

The sodium salt of β-keto ester **5** was formed by initial reaction with sodium hydride in hexamethylphosphoramide at room temperature. Addition of chloromethyl methyl ether gave rise to the methoxymethyl enol ether **10a** (ν_{max} 1710 and 1605 cm^{-1}) to the complete exclusion of the C-alkylated isomer. The nmr chemical shift for the methylene protons of the methoxymethyl group (AB system centered at τ 5.18; $\Delta\nu_{AB}$ = 30 Hz, J_{AB} = 6.0 Hz) is consistent only with the O-alkylated product.

The crude enol ether **10a** was submitted to reduction with lithium in liquid ammonia and the octalin ester **11** was obtained in 60% overall yield. Once again the less stable isomer was formed preferentially since equilibration produced the epimeric ester **12**. The nmr signal for the angular methyl group in **11** (τ 9.18) is shifted upfield with respect to **12** (τ 9.05). The methoxymethyl enol ether of β-keto ester **6** was also prepared by reaction of the sodium salt with chloromethyl methyl ether in hexamethylphosphoramide. Reduction of the crude enol ether (**7b**) with excess lithium in liquid ammonia gave ester **8** in 61% overall yield from **6**.

Since acylation of β-keto esters affords mainly O-acyl derivatives,[24] we also prepared the enol acetate derivative (**10b**) of β-keto ester **6**. Treatment of the sodium enolate with acetyl chloride in 1,2-dimethoxyethane produced exclusive O-acetylation to give **10b** in good yield. The infrared spectrum of **10b** shows absorption bands at 1770, 1715, and 1630 cm^{-1} representing the enol acetate carbonyl, the conjugated ester carbonyl, and the conjugated double bond, respectively. Reduction of unpurified **10b** with lithium in liquid ammonia provided ester **11** in 34% overall yield from **5**, a yield inferior to that obtained from reduction of the methoxymethyl enol ether **10a**.



Treatment of ester **11** with excessm ethyllithium in ether gave (±)-eremoligenol (**1**) in 81% yield. The

(17) D. S. Watt, J. M. McKenna, and T. A. Spencer, *J. Org. Chem.*, **32**, 2674 (1967).

(18) See also, M. Vandewalle and F. Compernolle, *Bull. Soc. Chim. Belg.*, **76**, 43 (1967).

(19) W. J. Gensler, C. D. Gatsonis, and Q. A. Ahmed, *J. Org. Chem.*, **33**, 2968 (1968), and references cited therein.

(20) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *ibid.*, **30**, 713 (1965).

(21) For a case of similar stereoselectivity, see W. G. Dauben and R. M. Coates, *J. Amer. Chem. Soc.*, **86**, 2490 (1964).

(22) (a) G. Brieger and W. M. Pelletier, *Tetrahedron Lett.*, 3555 (1965); (b) S. J. Rhoads and R. W. Hasbrouck, *Tetrahedron*, **22**, 3557 1966); (c) (c) A. L. Kurz, I. P. Beletskaya, A. Macías, and O. A. Reutov, *Tetrahedron Lett.*, 3679 (1968); (d) W. J. Le Noble and J. E. Puerta, *ibid.*, 1097 (1966); (e) A. L. Kurtz, I. P. Beletskaya, A. Macías, and S. S. Yafit, *J. Org. Chem. USSR*, **4**, 1327 (1968); (f) W. J. Le Noble and H. F. Morris, *J. Org. Chem.*, **34**, 1969 (1969).

(23) J. L. Simonsen and R. Storey, *J. Chem. Soc.*, 2106 (1909).

(24) J. P. Ferris, B. G. Wright, and C. C. Crawford, *J. Org. Chem.*, **30**, 2367 (1965).

infrared and nmr spectra of the synthetic eremoligenol are identical with those of naturally occurring (−)-eremoligenol.[4,25] The nmr spectrum of (±)-eremoligenol in chloroform-*d* shows the two methyl groups adjacent to the hydroxyl group as a six-proton singlet at τ 8.87. In pyridine these two methyl groups are shifted downfield to τ 8.71. The effect of pyridine on the chemical shifts of protons adjacent to hydroxyl groups has been studied previously.[26]

Dehydration of the synthetic eremoligenol with thionyl chloride in pyridine[4] gave (±)-eremophilene (**2**) and its double bond isomer **13** in a 2:1 ratio. The infrared and nmr (100 MHz) spectra of the synthetic eremophilene are identical with those of an authentic sample, (−)-eremophilene.[5,27] The glpc retention times of the synthetic and authentic eremophilene were also identical on two different columns. The nmr and infrared spectral data obtained for the double-bond isomer **13** are in agreement with those reported for **13** derived from naturally occurring (+)-valerianol (**3**).[6]

The reaction of ester **12** with excess methyllithium in ether furnished (±)-valerianol (**3**) in 84% yield. The infrared and nmr spectra of the synthetic valerianol are identical with those of an authentic sample of (+)-valerianol.[5,7,28] The glpc retention times of the synthetic and authentic valerianol were also identical on two different columns. Although the nmr spectrum of (±)-valerianol is very similar to that of (±)-eremoligenol the infrared spectra of these two isomers are easily distinguished.

Dehydration of the synthetic valerianol with thionyl chloride in pyridine[6,7] gave (±)-valencene (**4**) along with the double-bond isomer **13** in a 3:1 ratio. The infrared spectrum of synthetic valencene is identical with that of naturally occurring (+)-valencene.[6,8a,29] The chemical shifts in the nmr spectrum of synthetic valencene are the same as those reported for (+)-valencene except for the secondary methyl group which is a doublet centered at τ 9.10. This doublet has been previously reported at τ 9.05.[6] The refractive index of the synthetic valencene is the same as that reported for (+)-valencene.[6,8a] The infrared and nmr spectra of (±)-valencene are distinctly different from the corresponding spectra of (±)-eremophilene.

The syntheses of (±)-eremoligenol (**1**), (±)-eremophilene (**2**), (±)-valerianol (**3**), and (±)-valencene (**4**) provide a rigorous proof of the structure and stereochemistry of these sesquiterpenes. The total syntheses of valerianol and valencene also constitute the total syntheses of other eremophilane sesquiterpenes since (+)-valerianol has been previously converted to nootkatone and α-vetivone,[6,7] and (+)-valencene has also been converted to nootkatone.[8]

The transformation of **5** and **6** to esters **11** and **8**, respectively, indicates that the lithium–ammonia reduction of methoxymethyl enol ethers can serve as an effective method for selective removal of the ketone group in a β-keto ester. In addition, the generation of the less stable, axial stereoisomer permits the synthesis of either ester epimer. The scope of this two-step sequence has been examined with a series of simple β-keto esters; the results of this investigation will be presented in a separate paper.[30]

Experimental Section[31]

Methoxymethyl Enol Ether (10a) of Ethyl 8β,8aβ-Dimethyl-1-oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (5).—To a stirred mixture of 885 mg (22.0 mmol) of a 60% dispersion of sodium hydride in mineral oil and 80 ml of dry hexamethylphosphoramide at 5° under nitrogen was added a solution of 5.00 g (20.0 mmol) of β-keto ester **5**[9] in 20 ml of hexamethylphosphoramide. The mixture was stirred for 1.0 hr at room temperature. The solution was then cooled to 5°, and 1.93 g (24.0 mmol) of chloromethyl methyl ether was added. After stirring for 2.0 hr at room temperature, the solution was cooled to 0° and poured into 50 ml of ice-cold saturated sodium bicarbonate solution. The sodium bicarbonate solution was diluted with 50 ml of water and was then extracted with two 100-ml portions of petroleum ether (bp 30–60°). The petroleum ether solution was washed four times with 40–50-ml portions of water, dried with sodium sulfate, and evaporated under reduced pressure to give a yellow oil. Evaporation under reduced pressure gave 5.70 g of a yellow oil which was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column A, 183°, 200 ml/min) of the crude oil revealed a single peak. An analytical sample of enol ether **10a** was obtained by preparative glpc (column B, 190°): ir 1710 (C=O) and 1605 (conjugated double bond) cm^{-1}; nmr τ 4.63 (m, 1 H), 5.18 (AB, d, $\Delta\nu_{AB}$ = 30 Hz, J_{AB} = 6.0 Hz, $-OCH_2O-$), 5.91 (quartet, 2 H, J = 7.0 Hz), 6.53 (s, 3 H), 8.74 (t, 3 H, J = 7.0 Hz), and 8.82 (s, 3 H). The secondary methyl group is hidden by the absorption at τ 8.74 and 8.82.

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.51; H, 8.81.

Ethyl 8β,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2β-naphthoate (11) from Reduction of the Methoxymethyl Enol Ether 10a.—A solution of 5.70 g of the crude enol ether **10a** in 105 ml of ether was rapidly added to a magnetically stirred, dark blue solution of 750 mg (0.108 g-atom) of lithium in 330 ml of anhydrous ammonia under argon. Powdered Dry Ice was used to cool the reaction flask while the addition was made. After stirring for 12 min at the liquid ammonia boiling point (−33°), the reaction flask was again cooled with powdered Dry Ice for 10 min, and then 30 g of ammonium chloride was added essentially all at once to quench. The blue color of the solution actually faded 2 min before quenching. After 250 ml of ether was added, the Dry Ice–isopropyl alcohol condenser was replaced with a sodium hydroxide drying tube. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The mixture was then filtered, and the inorganic salts were crushed and washed

(25) Copies of the infrared (film) and nmr ($CDCl_3$ and pyridine) spectra of (−)-eremoligenol were furnished by Dr. H. Ishii (Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan), to whom we are most grateful.

(26) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

(27) This sample of (−)-eremophilene was generously donated by Professor V. Herout (Czechoslovak Academy of Science, Institute of Organic Chemistry and Biochemistry, Flemingovo Nam. 2, Prague, Czechoslovakia).

(28) We wish to thank Professor G. Jommi (Institute of Organic Chemistry, University of Milano, Milano, Italy) and Dr. H. Hikino (Pharmaceutical Institute, Tohoku School of Medicine, Kitu-4-bancho, Sendai, Japan) for samples of (+)-valerianol.

(29) An infrared spectrum of (+)-valencene was kindly provided by Professor V. Herout.

(30) R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2601 (1970).

(31) All melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 137 or Model 521 spectrometer in carbon tetrachloride solution unless otherwise specified and were calibrated with the polystyrene band at 1603 cm^{-1}. Proton magnetic resonance spectra were determined with a Varian Associates Model A-60A or A-56-60 spectrometer using tetramethylsilane as an internal standard. A Varian Associates Model HA-100 spectrometer was used where indicated. All nmr spectra were determined in carbon tetrachloride solution unless otherwise specified. Mass spectra were determined on an Atlas CH4 mass spectrometer. Microanalyses were determined in the University of Illinois microanalytical laboratory. Gas chromatography (glpc) was performed on a Wilkens Aerograph A-90-P instrument employing helium as the carrier gas. The following columns were used: a 5 ft × 0.25 in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column A), a 6 ft × $^3/_8$ in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column B), a 5 ft × 0.25 in. column of 3% SE-30 on 60–80 mesh Chromosorb W (column C), a 6 ft × 0.25 in. column of 15% Carbowax 20M on 60–80 mesh Chromosorb W (column D), a 6 ft × $^3/_8$ in. column of 15% Carbowax 20M on 60–80 mesh Chromosorb W (column E), and a 5 ft × 0.25 in. column of 15% FFAP on 60–80 mesh Chromosorb W (column F).

three times with ether. The ether solution was then evaporated under reduced pressure to give 4.65 g of a slightly yellow oil. Glpc analysis (column B, 165°, 200 ml/min) of this oil revealed that there was essentially only one volatile component. Chromatography of the crude product on 80 g of Woelm neutral alumina (activity II) and elution with 0–10% ether in petroleum ether (bp 30–60°) gave 2.85 g (60% from β-keto ester 5) of ester 11 as a colorless oil. An analytical sample was obtained by preparative glpc (column B, 165°): n^{25}D 1.4905; ir 1729 (C=O), 1460, 1375, 1200, 1176, 1100, 1063, and 1045 cm^{-1}; nmr τ 4.73 (m, 1 H), 5.90 (quartet, 2 H, J = 7.0 Hz), 8.74 (t, 3 H, J = 7.0 Hz), 9.12 (d, 3 H, J = 6.0 Hz), and 9.18 (s, 3 H).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.22; H, 10.18.

Ethyl 8β,8aβ-Dimethyl-1-acetoxy-3,4,6,7,8a-hexahydro-2-naphthoate (10b).—To a stirred mixture of 354 mg (8.83 mmol) of a 60% dispersion of sodium hydride in mineral oil and 27 ml of 1,2-dimethoxyethane at 0° under nitrogen was added dropwise over a period of 20 min a solution of 2.00 g (8.00 mmol) of β-keto ester 5 in 5 ml of 1,2-dimethoxyethane. After stirring an additional 20 min at room temperature, 754 mg (9.60 mmol) of acetyl chloride was added, and the solution was then stirred at room temperature for 30 min. The solution was then cooled and poured into 50 ml of an ice-cold saturated sodium bicarbonate solution. The petroleum ether (bp 30–60°) extract was washed with water until neutral, dried with sodium sulfate, and evaporated to give 2.38 g of enol acetate 10b which was used without any further purification. An analytical sample was obtained by preparative glpc (column B, 188°): ir 1770 (C=O), 1715 (C=O), and 1629 (conjugated double bond) cm^{-1}; nmr τ 4.58 (m, 1 H), 5.94 (quartet, 2 H, J = 7.0 Hz), 7.89 (s, 3 H), 8.78 (t, 3 H, J = 7.0 Hz), 8.88 (s, 3 H), and 8.89 (d, 3 H, J = ~6 Hz).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.63; H, 8.32.

Ester 11 from Reduction of the Enol Acetate 10b.—To a stirred solution of 300 mg (0.0432 g-atom) of lithium in 132 ml of anhydrous ammonia under argon was added a solution of 2.38 g of the crude enol acetate 10b in 42 ml of ether. After stirring for 35 min, the solution was cooled for 10 min in powdered Dry Ice, and then 12 g of ammonium chloride was added, and the Dry Ice–isopropyl alcohol condenser was replaced with a sodium hydroxide drying tube. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The mixture was then filtered, and the inorganic salts were washed with more ether. The ether solution was then evaporated to give 1.80 g of a yellow oil which was chromatographed on 55 g of Woelm neutral alumina (activity II). Elution with 0–10% ether in petroleum ether (bp 30–60°) gave 640 mg (34% from β-keto ester 5) of ester 11 as a colorless oil which had infrared and nmr spectra identical with those previously reported.

(±)-Eremoligenol (1).—Methyllithium was prepared by adding 3.62 g (25.5 mmol) of methyl iodide to 0.354 g (0.0510 g-atom) of small lithium pieces in 21 ml of anhydrous ether under argon at such a rate that there was only very mild refluxing of the ether. After the addition was completed, the solution was stirred an additional 0.5 hr. To the stirred methyl lithium solution under argon was slowly added a solution of 600 mg (2.54 mmol) of ester 11 in 3 ml of ether. After stirring for 2.5 hr at room temperature, the solution was cooled in ice water and poured into an ice-cold solution of 3 g of ammonium chloride in 45 ml of water. The petroleum ether (bp 30–60°) extract was washed with water until neutral, dried with sodium sulfate, and evaporated to give 570 mg of a slightly yellow oil which was then chromatographed on 15 g of Woelm neutral alumina (activity III). Elution with 25% ether in petroleum ether (bp 30–60°) gave 457 mg (81%) of (±)-eremoligenol (1) as a colorless viscous oil. Alternatively, the alcohol could be purified by preparative glpc (column A, 157°). The infrared (film) and nmr ($CDCl_3$ or pyridine) spectra of the synthetic eremoligenol were identical with the corresponding spectra of authentic (−)-eremoligenol.[4,25]

(±)-Eremophilene (2).—To a solution of 300 mg (1.35 mmol) of (±)-eremoligenol (1) in 1.8 ml of pyridine at 0° was added 300 mg (2.5 mmol) of thionyl chloride.[4] After stirring for 15 min at 0°, the solution was poured into ice-cold water. The ether extract was washed with 10% concentrated hydrochloric acid, saturated sodium bicarbonate, and water, dried with sodium sulfate, and evaporated to give 270 mg of a yellow oil. Glpc analysis (column A, 136°, 200 ml/min) of the oil revealed that it was a 2:1 mixture of two compounds. Preparative glpc (column B, 128°) of the major component which had the shorter retention time gave 78 mg (28%) of (±)-eremophilene (2) as a colorless oil. The synthetic eremophilene was identified by comparison of its infrared and 100-MHz nmr spectra with those of an authentic sample of (−)-eremophilene.[5,27] Glpc retention times (column A, 118°, 200 ml/min, and column F, 118°, 125 ml/min) of the synthetic and authentic samples were also identical. Preparative glpc of the minor component gave 38 mg (14%) of the double bond isomer 13 as a colorless oil which gave infrared and nmr spectral data in agreement with those reported for 13.[6]

Ethyl 8β,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2α-naphthoate (12).—To a solution of sodium ethoxide prepared from 1.90 g (0.082 g-atom) of sodium and 100 ml of absolute ethanol was added a solution of 1.40 g (6.00 mmol) of ester 11 in 10 ml of absolute ethanol. After refluxing for 45 min under nitrogen, the solution was cooled and poured into ice cold water, and the basic aqueous solution was washed with water, dried with sodium sulfate, and evaporated to give 1.26 g of a yellow oil. The crude oil was chromatographed on 40 g of Woelm neutral alumina (activity II). Elution with 0–10% ether in petroleum ether (bp 30–60°) gave 988 mg (71%) of ester 12 as a colorless oil: ir 1731 (C=O), 1457, 1375, 1307, 1177, 1163, and 1034 cm^{-1}; nmr τ 4.72 (m, 1 H), 5.96 (quartet, 2 H, J = 7.0 Hz), 8.78 (t, 3 H, J = 7.0 Hz), 9.05 (s, 3 H), and 9.09 (d, 3 H, J = ~6 Hz). The nmr spectrum indicated that no ester 11 was present in the product. An analytical sample was obtained by preparative glpc (column B, 155°).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.27; H, 10.07.

(±)-Valerianol (3).—Methyllithium was prepared by adding 3.62 g (25.5 mmol) of methyl iodide to 0.354 g (0.0510 g-atom) of small lithium pieces in 21 ml of anhydrous ether under argon at such a rate that there was only very mild refluxing of the ether. After the addition was completed, the solution was stirred an additional 0.5 hr. To the stirred methyllithium solution under argon was slowly added a solution of 600 mg (2.54 mmol) of ester 12 in 3 ml of ether. After stirring for 2.5 hr at room temperature, the solution was cooled in ice water and poured into an ice-cold solution of 3 g of ammonium chloride in 45 ml of water. The petroleum ether (bp 30–60°) extract was washed with water until neutral, dried with sodium sulfate, and evaporated to give 595 mg of a slightly yellow oil which was chromatographed on 15 g of Woelm neutral alumina (activity III). Elution with 25% ether in petroleum ether (bp 30–60°) gave 472 mg (84%) of (±)-valerianol (3) as a colorless viscous oil. Alternatively, the alcohol could be purified by preparative glpc (column B, 156°). The synthetic valerianol was identified by comparison of its infrared (film) and nmr ($CDCl_3$) spectra with those of an authentic sample of (−)-valerianol provided by Dr. G. Jommi.[6,28] In the nmr spectrum of the synthetic valerianol the absorption at τ 8.65 is due to the hydroxyl proton since it disappears upon addition of D_2O. The infrared spectrum of the synthetic valerianol also appeared to be identical with that of a sample of (+)-valerianol provided by Dr. H. Hikino;[7,28] however, there were some minor impurities in this authentic sample. The glpc retention times (column A, 148°, 150 ml/min, and column D, 164°, 125 ml/min) of the synthetic and two authentic samples were also identical.

(±)-Valencene (4).—To a solution of 300 mg (1.35 mmol) of (±)-valerianol in 1.8 ml of pyridine was added 300 mg (2.5 mmol) of thionyl chloride. After stirring for 12 min at 0°, the solution was poured into 12 ml of ice water. The petroleum ether (bp 30–60°) extract was washed with 10% concentrated hydrochloric acid, saturated sodium bicarbonate, and water, dried with sodium sulfate, and evaporated to give 278 mg of a yellow oil. Glpc analysis (column A, 152°, 100 ml/min) of the oil revealed that it was a 3:1 mixture of two compounds. Preparative glpc (column A, 152°) of the major component which had the shorter retention time gave 121 mg (44%) of (±)-valencene (4) as a colorless oil; n^{20}D 1.5070 (lit.[7,9] n^{20}D 1.5073, 1.5075). The infrared spectrum of the synthetic valencene appeared to be identical with the infrared spectrum of (+)-valencene published by Hunter and Brogden[8a] and a spectrum of (+)-valencene.[6,29] The chemical shifts of the nmr ($CDCl_3$) spectrum of the synthetic valencene are the same as those reported for valencene derived from (+)-valerianol except for the secondary methyl group which is a doublet centered at τ 9.10. This doublet has been previously reported at τ 9.05.[6] Preparative glpc of the minor component gave 37 mg (14%) of the double-bond isomer 13 as a colorless oil which gave infrared and nmr spectral data in agreement with reported values.[6]

Methoxymethyl Enol Ether (7b) of Ethyl 8α,8aβ-Dimethyl-1-

oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (6).—The procedure was identical with that described for the methoxymethyl enol ether **10a**. Reaction of 5.00 g (20.0 mmol) of β-keto ester **6**[9] gave 5.60 g of the crude methoxymethyl enol ether as a yellow oil. This material was used in the lithium–ammonia reduction step without further purification. Glpc analysis (column A, 178°, 200 ml/min) of the crude product revealed a single peak. The infrared spectrum of the crude enol ether showed bands at 1710 (C=O) and 1610 (conjugated double bond) cm^{-1}.

Ethyl 8α,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2β-naphthoate (8) by Reduction of Methoxymethyl Enol Ether 7b.—The procedure was idential with that described for the reduction of the methoxymethyl enol ether **10a**. Reduction of 5.60 g of the crude methoxymethyl enol ether **7b** with 750 mg (0.108 g-atom) of lithium gave 4.76 g of a yellow oil which showed a single peak on glpc analysis (column A, 163°, 200 ml/min). Chromatography of the crude product on 80 g of Woelm neutral alumina (activity II) and elution with 10% ether in petroleum ether (bp 30–60°) gave 2.86 g (61% from β-keto ester **6**) of ester **8** as a colorless oil. An analytical sample was obtained by preparative glpc (column B, 168°): $n^{25}D$ 1.4907; ir 1729 (C=O), 1193, and 1041 cm^{-1}; nmr τ 4.68 (m, 1 H), 5.88 (quartet, 2 H, J = 7.0 Hz), 8.73 (t, 3 H, J = 7.0 Hz), 9.01 (s, 3 H), and 9.07 (d, 3 H, J = ~7 Hz).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.09; H, 10.07.

Ester 8 by Reduction of the Methyl Enol Ether 7a.—The procedure was similar to that used in the reduction of methoxymethyl enol ether **10a**. A solution of 350 mg (1.33 mmol) of the methyl enol ether **7a**[9] was added with stirring to a dark blue solution of 50 mg (0.0072 g-atom) of lithium in 22 ml of anhydrous ammonia under argon. The solution was stirred for 1.0 hr at the liquid ammonia boiling point and was then cooled in powdered Dry Ice before quenching with 2.0 g of ammonium chloride. After addition of 25 ml of ether, evaporation of the ammonia, filtration, and evaporation of the ether, 312 mg of a slightly yellow oil was obtained. Glpc analysis (column A, 166°, 200 ml/min) revealed that there was essentially only one peak. Purification of the oil by preparative glpc (column B, 167°) gave 210 mg (67%) of ester **8** which was found to be identical with that obtained above.

Ethyl 8α,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2α-naphthoate (9).—To a solution of sodium ethoxide prepared from 280 mg (0.012 g-atom) of sodium and 17 ml of absolute ethanol was added a solution of 200 mg (0.85 mmol) of ester **8** in 3 ml of ethanol. After refluxing for 1.25 hr under nitrogen, the solution was cooled and poured into ice-cold water, and the resulting basic aqueous solution was extracted with petroleum ether (bp 30–60°). The petroleum ether extract was washed with water, dried with sodium sulfate, and evaporated to give 202 mg of a yellow oil. Preparative glpc (column B, 162°) of the oil gave 65 mg (33%) of ester **9** as a colorless oil: ir 1730 cm^{-1} nmr τ 4.70 (m, 1 H), 5.96 (quartet, 2 H, J = 7.0 Hz), 8.79 (t, 3 H, J = 7.0 Hz), 8.88 (s, 3 H), and 9.07 (d, 3 H, J = 6.5 Hz). The glpc and nmr data showed that no ester **8** remained after equilibration.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.02; H, 10.27.

Registry No.—(±)-Eremoligenol, 22343-25-5; (±)-eremophilene, 22343-24-4; (±)-valerianol, 24741-63-7; (±)-valencene, 24741-64-8; **7b**, 24799-48-2; **8**, 24744-07-8; **9**, 24744-08-9; **10a**, 24744-09-0; **10b**, 24744-10-3; **11**, 22343-27-7; **12**, 24744-12-5.

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Reduction of β-Keto Ester Methoxymethyl Enol Ethers to Saturated Esters with Lithium in Liquid Ammonia[1]

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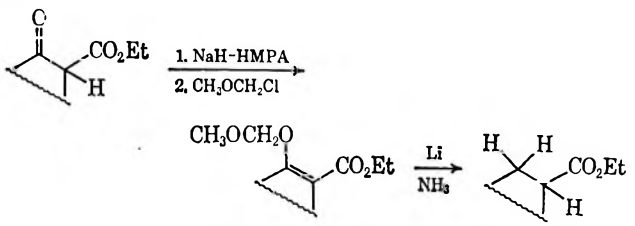
Methoxymethylation of a series of β-keto esters in hexamethylphosphoramide gave, with one exception, high proportions (96–100%) of O-alkylation. The reduction of the enol ethers with lithium in liquid ammonia furnished the corresponding saturated esters in variable overall yields (23–61%). This new method for reducing the ketone group of a β-keto ester is apparently most efficient with relatively hindered compounds.

We have recently described a new synthetic procedure for the reduction of a β-keto ester to a saturated ester.[3] The method consists of first conversion to the methoxymethyl enol ether by alkylation of the sodium salt of the β-keto ester with chloromethyl methyl ether in hexamethylphosphoramide. The enol ether without purification is then subjected to reaction with lithium in liquid ammonia which effects a "double" reduction to the saturated ester.



In order to explore the generality of this method, we have applied the two-step sequence to a series of cyclic and acyclic β-keto esters. The results of this investigation are summarized in Table I.

In all cases except ethyl 2-*n*-butylacetoacetate (**15**), the reaction of the sodium enolate with chloromethyl methyl ether produced essentially exclusive O-alkylation. When less polar aprotic solvents were used instead of hexamethylphosphoramide, the amount of O-alkylated product decreased. In hexamethylphosphoramide the relative percentages of O- and C-alkylation for 2-carbethoxycyclohexanone (**5**) were 97 and 3%, respectively, but in 1,2-dimethoxyethane the corresponding values were 75 and 25%. In dimethyl sulfoxide there was 90% O-alkylation and 10% C-alkylation. The effect of the alkylating agent in promoting O-alkylation can be seen by comparison with results reported by other workers.[4] Alkylation of the sodium enolate of ethyl acetoacetate (**11**) in hexa-

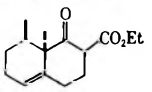
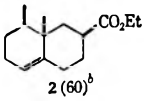
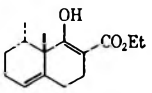
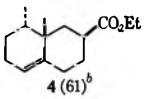
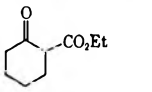
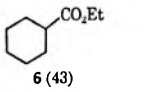
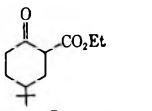
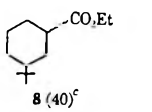
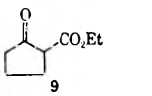
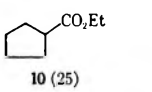
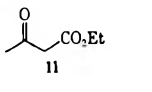
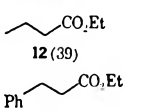
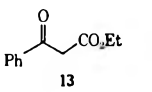
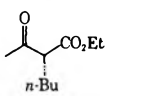
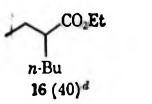
(1) Taken in part from Ph.D. Thesis of J. E. S., University of Illinois, Urbana, 1969.

(2) National Science Foundation Trainee, 1965–1969.

(3) R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2597 (1970); see also *Tetrahedron Lett.*, 5405 (1968).

(4) A. L. Kurz, I. P. Beletskaya, A. Macías, and O. A. Reutov, *Tetrahedron Lett.*, 3679 (1968).

TABLE I
PREPARATION AND REDUCTION OF METHOXYMETHYL ENOL ETHERS OF VARIOUS β-KETO ESTERS

β-Keto ester	Methoxymethyl enol ether, O/C ratio (yield, %)	Reduction product, (overall yield,[a] %)
 1	100/0[b]	 2 (60)[b]
 3	100/0[b]	 4 (61)[b]
 5	97/3 (82)	 6 (43)
 7	96/4 (79)	 8 (40)[c]
 9	97/3 (92)	 10 (25)
 11	100/0 (84)	 12 (39)
 13	98/2	14 (23)
 15	69/31	 16 (40)[d]

[a] From the β-keto ester. [b] For details see reference in footnote 3. [c] *trans* to *cis* isomer ratio, 70:30. [d] Yield in this case from the methoxymethyl enol ether.

methylphosphoramide with ethyl chloride at room temperature has been reported to give 60 and 40% of the O- and C-alkylation products respectively. As shown in Table I, alkylation of ethyl acetoacetate with chloromethyl methyl ether gave only the O-alkylated product.[5]

The infrared spectra of the various methoxymethyl enol ethers show bands at approximately 1715 and 1635 cm^{-1} for the conjugated ester carbonyl and conjugated double bond, respectively. In the case of the acyclic enol ethers there is the possibility of *cis* and *trans* isomerism about the double bond. However, the nmr spectra indicate that only one isomer is present in each case. This isomer may be the *trans* if chelation to the sodium ion in the enolate anion is an important stabilizing factor. The nmr spectra of the methoxymethyl enol ethers of 2-carbethoxycyclohexanone (**5**), 2-carbethoxy-4-*t*-butylcyclohexanone (**7**), and 2-carbethoxycyclopentanone (**9**) show the methylene group bonded to the two oxygen atoms as singlets at τ 5.13, 5.13, and 5.02, respectively. The enol ethers of ethyl acetoacetate (**11**), ethyl benzoylacetate (**15**), and ethyl 2-*n*-butylacetoacetate (**13**) show two-proton singlets at τ 5.02, 4.89, and 5.01, respectively. The similarity of these chemical shifts in both the cyclic and acyclic enol ethers provides some support for a *trans* geometry in the acyclic enol ethers. In the nmr spectra of the C-alkylated isomers from **5** and **15**, the methylene groups bonded to the methoxy groups appear as AB doublets at higher field centered at τ 6.44 (J_{AB} = 9 Hz, $\Delta\nu_{AB}$ = 13 Hz) and τ 6.37 (J_{AB} = 9.5 Hz, $\Delta\nu_{AB}$ = 6.5 Hz), respectively. The nonequivalence of the two geminal protons can be attributed to the asymmetric molecular environment.

Reduction of the methoxymethyl enol ethers of the various β-keto esters with excess lithium in liquid ammonia gave the products and yields shown in Table I. The ester products listed were essentially the only compounds found upon glpc analysis of the somewhat viscous crude products. Since the weights of the crude products corresponded to the theoretical amount, the remainder of the material must have been relatively nonvolatile substance. Dimeric or polymeric materials could be formed by coupling of anion radical intermediates or by acylation of anion radicals with other ester molecules.[6,7] In the cases of the enol ethers of the bicyclic β-keto esters **1** and **3**, steric hindrance might suppress such intermolecular reactions thus accounting for the higher yields of the reduced esters.

Lithium–ammonia reduction of ethyl cinnamate gave an 18% yield of ethyl hydrocinnamate (**14**). This is close to the 23% yield of ethyl hydrocinnamate obtained by lithium–ammonia reduction of the methoxymethyl enol ether of ethyl benzoylacetate (**13**) and indicated that the enol ether leaving group ($-OCH_2OCH_3$) was not responsible to any great extent for the low yield of ester product. However, lithium–ammonia reduction of *trans*-cinnamic acid gave a 65% yield of hydrocinnamic acid.[8] This difference in yields could be due to elimination of intermolecular acylation in the reduction of the acid or alternatively the repression of coupling between the doubly charged dianion radical intermediates from cinnamic acid. When the methoxymethyl enol ether of 2-carbethoxycyclohexanone was reduced in the presence of one equivalent of *t*-butyl alcohol in hopes of decreasing the amount of intermolecular side reactions, "overreduction" occurred to give primary alcohol in addition to the normal ester product. Apparently the *t*-butyl alcohol protonates the enolate anion of the ester, and then the ester can be further reduced with excess lithium to the primary alcohol. The combined yield of alcohol and ester was approximately the same as the yield of the ester in the absence of *t*-butyl alcohol. Primary alcohol was also produced if too much lithium was used in the reductions. The alcohol is probably formed when the reaction is quenched with ammonium chloride.[9]

In the reduction of the methoxymethyl enol ether of ethyl 2-carbethoxy-4-*t*-butylcyclohexanone (**7**), glpc analysis of the crude product revealed that the relative percentages of *trans* and *cis* ethyl 3-*t*-butylcyclohexanecarboxylate (**8**) were 70 and 30%, respectively. Evi-

(5) See also J. L. Simonsen and R. Storey, *J. Chem. Soc.*, 2106 (1909).

(6) *Cf.* R. G. Carlson and R. G. Blecke, *Chem. Commun.*, 93 (1969).

(7) The possibility that ester was being lost owing to reaction with ammonia after quenching with ammonium chloride was eliminated by the observation that ethyl cyclohexanecarboxylate could be completely recovered after it was added in ether to a solution of ammonia and ammonium chloride.

(8) This result suggests that prior hydrolysis of the enol ether ester to the acid then reduction might improve the yields. We have not had the opportunity to investigate this possibility.

(9) D. S. Watt, J. M. McKenna, and T. A. Spencer, *J. Org. Chem.*, **32**, 2674 (1967).

dence that the major isomer had the carbethoxy group axial and *trans* to the equatorial *t*-butyl group was obtained by equilibration with sodium ethoxide in ethanol to a mixture consisting of 25% *trans* and 75% *cis* ethyl 3-*t*-butylcyclohexanecarboxylate. The predominance of the *trans* (axial) ester in the reduction product mixture indicates a significant preference for equatorial protonation even in the absence of an opposing axial substituent as in the bicyclic esters. This result contrasts with the absence of selectivity found in the protonation of the enolate anion of 4-*t*-butylacetylcyclohexane with acetic acid,[10] but is comparable with the selectivity (60–65% equatorial protonation) observed in the ketonization of the enol of 4-phenylacetylcyclohexane with ammonium chloride as proton donor.[11]

It should be pointed out that other enol derivatives of β-keto esters will undergo this reduction in lithium–ammonia solutions. The enol acetate of the bicyclic β-keto ester **1** was reduced to the same octalin ester (**2**) but in substantially lower yield (34% overall).[3] The methyl enol ether of **3** was converted to ester **4** in 67% yield,[3] an efficiency comparable to that obtained with the methoxymethyl analog. Since the preparation of methyl (or other alkyl) enol ethers is more likely to be complicated by C-alkylation,[12] the use of the methoxymethyl enol ether appears to be preferable.

The range in the overall yields (23 to 61%) of the saturated esters in the two-step sequence is evidently due mostly to the variations in the lithium–ammonia reduction step. Since the yields are best with the hindered β-keto esters, the method should provide a useful complement to existing chemical procedures.[13] In addition the generation of the less stable ester epimer (*e.g.*, from **1** and **3**) may be of stereochemical advantage.

Experimental Section[14]

2-Carbethoxycyclohexanone Methoxymethyl Enol Ether.—To a cooled mixture of 1.32 g (33.0 mmol) of 60% dispersion of sodium hydride in mineral oil and 90 ml of dry hexamethylphosphoramide under nitrogen was added a solution of 5.10 g (30.0 mmol) of 2-carbethoxycyclohexanone (**5**) in 10 ml of hexamethylphosphoramide. The solution was stirred for 1.0 hr at room temperature. The solution was then cooled, and 2.90 g (36.0 mmol) of chloromethyl methyl ether was added with stirring. After 2.0 hr at room temperature the solution was cooled and poured into 50 ml of ice-cold saturated sodium bicarbonate solution. The sodium bicarbonate solution was diluted with 50 ml of water and was then extracted with two 100 ml-portions of ether. The ether solution was washed three times with 40–50-ml portions of water, dried with sodium sulfate, and evaporated under reduced pressure to give a yellow liquid. The liquid was mixed with 25 ml of petroleum ether (bp 30–60°) and was dried a second time with sodium sulfate. Evaporation under reduced pressure gave 6.60 g of the crude methoxymethyl enol ether as a yellow liquid which was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column B, 145°, 200 ml/min) of the crude product revealed that it consisted of 97% of the methoxymethyl enol ether and 3% of the C-alkylated isomer and that the actual yield of the enol ether was 82%. An anaytical sample of the C-alkylated isomer which had the shorter retention time was obtained by preparative glpc (column B, 137°). The infrared spectrum shows bands at 1715 (C=O) and 1740 (C=O) cm^{-1}. The nmr spectrum has absorptions at τ 5.84 (quartet, 2 H, J = 7.0 Hz), 6.72 (s, 3 H), and 8.74 (t, 3 H, J = 7.0 Hz). The methylene group bonded to the methoxy group appears as an AB system centered at τ 6.44 (J_{AB} = 9.0 Hz, $\Delta\nu_{AB}$ = 13 Hz).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.57; H, 8.25.

An analytical sample of the methoxymethyl enol ether was also obtained by preparative glpc (column B, 137°): $n^{20}D$ 1.4777; ir 1715 (C=O) and 1635 (conjugated C=C) cm^{-1}; nmr τ 5.13 (s, 2 H), 5.92 (quartet, 2 H, J = 7.0 Hz), 6.61 (s, 3 H), and 8.75 (t, 3 H, J = 7.0 Hz).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.75; H, 8.33.

When the above reaction was performed in the same manner except that 1,2-dimethoxyethane or dimethyl sulfoxide was used as the solvent instead of hexamethylphosphoramide, the amount of C-alkylation increased. In 1,2-dimethoxyethane there was 25% C-alkylation and 75% O-alkylation. In dimethyl sulfoxide there was 10% C-alkylation and 90% O-alkylation.

Reduction of 2-Carbethoxycyclohexanone Methoxymethyl Enol Ether.—A solution of 1.10 g of the crude methoxymethyl enol ether in 26 ml of ether was rapidly added to a magnetically stirred, dark blue solution of 250 mg (0.036 g-atom) of lithium in 82 ml of anhydrous ammonia under agron. Powdered Dry Ice was used to cool the reaction flask while this addition was made. After stirring for 12 min at the liquid ammonia boiling point (−33°), the solution was cooled for 6 min with powdered Dry Ice, and then 7.5 g of ammonium chloride was added essentially all at once to quench. The blue color of the solution actually faded 2 min before quenching. After 60 ml of ether was added, the Dry Ice–isopropyl alcohol condenser was replaced with a sodium hydroxide drying tube. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The mixture was then filtered, and the inorganic salts were crushed and washed three times with ether. The ether solution was then evaporated to give 940 mg of a slightly yellow liquid. Glpc analysis (column B, 100°, 150 ml/min) of this liquid revealed that there was essentially only one volatile compound. This compound was collected by preparative glpc (column B, 105°) and was found to be identical to ethyl cyclohexanecarboxylate (**6**) by comparison of infrared and nmr spectra and glpc retention times. The actual yield of ethyl cyclohexanecarboxylate was determined to be 321 mg (41% from β-keto ester **5**) by glpc (column B, 107°, 200 ml/min) using ethyl phenylacetate as an internal standard. A second reduction of the crude enol ether under the same conditions gave a 46% overall yield of **6**.

2-Carbethoxycyclopentanone Methoxymethyl Enol Ether.—Reaction[15] of 4.68 g (30.0 mmol) of 2-carbethoxycyclopentanone (**9**) gave 6.20 g of the crude methoxymethyl enol ether as a yellow liquid. This material was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column A, 140°, 150 ml/min) of the crude product revealed that it consisted of 97% of the methoxymethyl enol ether and 3% of the C-alkylated isomer and that the actual yield of the enol ether was 92%. The C-alkylated isomer which had the shorter retention time was obtained as a colorless liquid by preparative glpc (column B, 133°) and was characterized only by its infrared spectrum which shows bands at 1755 (C=O) and 1730 (C=O)

(10) H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).

(11) H. E. Zimmerman and P. S. Mariano, *J. Amer. Chem. Soc.*, **90**, 6091 (1968).

(12) G. Brieger and W. M. Pelletier, *Tetrahedron Lett.*, 3555 (1965); W. J. le Noble and J. E. Puerta, *ibid.*, 1087 (1966); S. J. Rhoads and R. W. Hasbrouch, *Tetrahedron*, **22**, 3557 (1966); W. J. le Noble and H. F. Morris, *J. Org. Chem.*, **34**, 1969 (1964); A. L. Kurta, I. P. Beletskaya, A. Macías, and S. S. Yafit, *J. Org. Chem. USSR*, **4**, 1327 (1968); S. J. Rhoads and R. W. Holder, *Tetrahedron*, **25**, 5443 (1969).

(13) (a) Clemmenson reduction: A. Afonso, *J. Amer. Chem. Soc.*, **90**, 7375 (1968). (b) Thioketal desulfurization: G. Stork and J. W. Schulenberg, *ibid.*, **84**, 284 (1962); T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); K. Mori and M. Matsui, *Tetrahedron*, **24**, 3095 (1968).

(14) Infrared spectra were recorded with a Perkin-Elmer Model 137 or Model 521 spectrometer. Carbon tetrachloride solutions were used unless otherwise specified and were calibrated with the polystyrene band at 1603 cm^{-1}. Nmr spectra were determined in carbon tetrachloride solution with a Varian Associates Model A-60A or A-56-60 spectrometer using tetramethylsilane as an internal standard. Microanalyses were determined in the University of Illinois microanalytical laboratory. Gas chromatography (glpc) was performed on a Wilkens Aerograph A-90-P instrument employing helium as the carrier gas. The following columns were used: a 5 ft × 0.25 in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column A), a 6 ft × ⅜ in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column B), a 5 ft × 0.25 in. column of 3% SE-30 on 60–80 mesh Chromosorb W (column C).

(15) The detailed procedure described for the preparation (or reduction) of the methoxymethyl enol ether of 2-carbethoxycyclohexanone was followed.

cm^{-1}. An analytical sample of the methoxymethyl enol ether was obtained by preparative glpc (column B, 133°): n^{20}D 1.4767; ir (film) bands at 1715 (C=O) and 1635 (conjugated C=C) cm^{-1}; nmr τ 5.02 (s, 2 H), 5.92 (quartet, 2 H, J = 7.0 Hz), 6.57 (s, 3 H), and 8.76 (t, 3 H, J = 7.0 Hz).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.08; H, 7.98.

Reduction of 2-Carbethoxycyclopentanone Methoxymethyl Enol Ether.—Reduction[15] of 1.02 g of the crude methoxymethyl enol ether with 250 mg (0.036 g-atom) of lithium gave 766 mg of a slightly yellow liquid which contained essentially only one volatile compound on glpc analysis (column B, 93°, 200 ml/min). This material was collected by preparative glpc (column B, 93°) and was shown to be identical to ethyl cyclopentanecarboxylate (10) by comparison of infrared spectra and glpc retention times. The actual yield of 10 was determined to be 177 mg (25%) from 9 by glpc (column B, 93°, 200 ml/min) using ethyl cyclohexanecarboxylate as an internal standard. A second reduction of the crude enol ether by the same procedure except that 210 mg of lithium was used gave a 11% overall yield of 10. When 275 mg of lithium was used, some ethyl cyclopentanecarboxylate was reduced to the primary alcohol, and the combined overall yield of ester and alcohol was 24%.

2-Carbethoxy-4-*t*-butylcyclohexanone Methoxymethyl Enol Ether.—Reaction[15] of 6.78 g (30.0 mmol) of 2-carbethoxy-4-*t*-butylcyclohexanone (7) gave 8.35 g of the crude methoxymethyl enol ether as a yellow liquid. This material was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column B, 183°, 200 ml/min) of the crude product revealed that it consisted of 96% of the methoxymethyl enol ether and 4% of the C-alkylated isomer and that the actual yield of the enol ether was 79%. The C-alkylated isomer which had the shorter retention time was obtained as a colorless liquid by preparative glpc (column B, 183°) and was characterized only by its infrared spectrum which shows bands at 1730 (C=O) and 1705 (C=O) cm^{-1}. An analytical sample of the methoxymethyl enol ether was obtained by preparative glpc (column B, 183°): n^{20}D 1.4772; ir (film) 1715 (C=O) and 1635 (conjugated C=C) cm^{-1}; nmr τ 5.13 (s, 2 H), 5.90 (quartet, 2 H, J = 7.0 Hz), 6.60 (s, 3 H), 8.74 (t, 3 H, J = 7.0 Hz), and 9.07 (s, 9 H).

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.66; H, 9.84.

Reduction of 2-Carbethoxy-4-*t*-butylcyclohexanone Methoxymethyl Enol Ether.—Reduction[15] of 1.38 g of the crude methoxymethyl enol ether with 240 mg (0.035 g-atom) of lithium gave 1.23 g of a slightly yellow liquid. Glpc analysis (column A, 138°, 200 ml/min) revealed that it consisted of 30% ethyl *cis*-3-*t*-butylcyclohexanecarboxylate (*cis*-8) and 70% ethyl *trans*-3-*t*-butylcyclohexanecarboxylate (*trans*-8). An analytical sample of the *trans* isomer which had the shorter retention time was obtained by preparative glpc (column B, 133°): n^{20}D 1.4522; ir (film) 1735 (C=O), 1200, 1180, 1160, 1145, and 1035 cm^{-1}; nmr τ 5.91 (quartet, 2 H, J = 7.0 Hz), 8.76 (t, 3 H, J = 7.0 Hz), and 9.14 (s, 9 H).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.24; H, 11.22.

An analytical sample of the *cis* isomer was also obtained by preparative glpc: n^{20}D 1.4535; ir (film) bands at 1735 (C=O), 1190, 1155, and 1040 cm^{-1}; nmr τ 5.95 (quartet, 2 H, J = 7.0 Hz), 8.77 (t, 3 H, J = 7.0 Hz), and 9.11 (s, 9 H).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.88; H, 11.42.

The combined actual yield of the *cis* and *trans* esters was determined to be 424 mg (40% from 7) by glpc (column B, 133°, 200 ml/min) using diethyl phthalate as an internal standard. When 200 mg (0.94 mmol) of the 70:30 mixture of *trans* and *cis* esters was refluxed for 35 min with a solution of sodium ethoxide prepared from 300 mg (0.013 g-atom) of sodium and 20 ml of absolute ethanol, the relative amounts of the *cis* and *trans* esters changed to 75 and 25%, respectively. Further heating at reflux did not change these percentages.

Ethyl Benzoylacetate Methoxymethyl Enol Ether.—Reaction[15] of 5.76 g (30.0 mmol) of ethyl benzoylacetate 13 gave 7.24 g of the crude methoxymethyl enol ether as a yellow liquid. This material was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column C, 160°, 150 ml/min) of the crude product revealed that it consisted of 98% the methoxymethyl enol ether and 2% an unidentified compound which was probably the C-alkylated isomer. Purification of the enol ether by preparative glpc (column A, 168°) was not possible owing to decomposition under the glpc conditions. The infrared spectrum (film) of the crude product shows bands at 1715 (C=O) and 1625 (conjugated C=C) cm^{-1}. The nmr spectrum shows absorptions at τ 4.40 (s, 1 H), 4.89 (s, 2 H), 5.89 (quartet, 2 H, J = 7.0 Hz), 6.49 (s, 3 H), and 8.73 (t, 3 H, J = 7.0 Hz).

Reduction of Ethyl Benzoylacetate Methoxymethyl Enol Ether.—Reduction[15] of 1.21 g of the crude methoxymethyl enol ether with 250 mg (0.036 g-atom) of lithium gave 958 mg of a viscous yellow liquid which contained only one volatile component on glpc analysis (column B, 121°, 150 ml/min). This material was collected by preparative glpc (column B, 129°) and was shown to be identical to ethyl hydrocinnamate (14) by comparison of infrared and nmr spectra. The actual yield of 14 was determined to be 196 mg (22% from 13) by glpc (column B, 121°, 150 ml/min) using ethyl phenylacetate as an internal standard. A second reduction of the crude enol ether by the same procedure, except that 210 mg of lithium was used, gave a 23% overall yield of ethyl hydrocinnamate. When 190 mg of lithium was used, the overall yield was 19%.

Ethyl 2-*n*-Butylacetoacetate Methoxymethyl Enol Ether.—Reaction[15] of 5.58 g (30.0 mmol) of ethyl 2-*n*-butylacetoacetate (15) gave 7.21 g of a yellow liquid. Glpc analysis (column A, 140°, 200 ml/min) of the crude product revealed that it consisted of 69% the methoxymethyl enol ether and 31% the C-alkylated isomer. An analytical sample of the C-alkylated isomer which had the shorter retention time was obtained by preparative glpc (column B, 152°): ir (film) 1740 (C=O) and 1715 (C=O) cm^{-1}; τ 5.85 (quartet, 2 H, J = 7.0 Hz), AB system centered at 6.37 (-OCH$_2$O-, J_{AB} = 9.5 Hz, $\Delta\nu_{AB}$ = 6.5 Hz), 6.70 (s, 3 H), 7.92 (s, 3 H), 8.73 (t, 3 H, J = 7.0 Hz), and 9.08 (t, 3 H, J = ~6 Hz).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.90; H, 9.57.

An analytical sample of the methoxymethyl enol ether was also obtained by preparative glpc: n^{20}D 1.4567; ir (film) 1710 (C=O) and 1630 (conjugated C=C) cm^{-1}; nmr τ 5.01 (s, 2 H), 5.90 (quartet, 2 H, J = 7.0 Hz), 6.59 (s, 3 H), 7.68 (s, 3 H), 8.73 (t, 3 H, J = 7.0 Hz), and 9.09 (t, 3 H, J = ~6 Hz).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.75; H, 9.65.

An attempt to purify the enol ether by distillation using a Vigreux column was only partially successful. Column chromatography on Woelm neutral alumina (activity II) and elution with 0–2% ether in petroleum ether (bp 30–60°) gave the pure methoxymethyl enol ether.

Reduction of Ethyl 2-*n*-Butylacetoacetate Methoxymethyl Enol Ether.—Reduction[15] of 1.15 g (5.00 mmol) of the purified methoxymethyl enol ether with 250 mg (0.036 g-atom) of lithium gave 862 mg of a yellow liquid which contained essentially only one volatile compound as shown by glpc analysis (column B, 112°, 120 ml/min). This compound was collected by preparative glpc (column B, 108°) and found to be identical with ethyl 2-ethylhexanoate (16) by comparison of infrared and nmr spectra. The actual yield of (16) was determined by glpc (column B, 112°, 120 ml/min) to be 40% based on the enol ether. When the methoxymethyl enol ether was reduced with 275 mg of lithium by the same procedure, some ethyl 2-ethylhexanoate was reduced to the primary alcohol, and the combined yield of ester and alcohol was 43%.

Ethyl Acetoacetate Methoxymethyl Enol Ether.—Reaction[15] of 3.90 g (30.0 mmol) of ethyl acetoacetate (11) gave 5.34 g of the crude methoxymethyl enol ether as a yellow liquid. This material was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column B, 114°, 120 ml/min) of the liquid revealed that it consisted of only the methoxymethyl enol ether and that the yield of the enol ether was 84%. An analytical sample of this material was obtained by preparative glpc (column B, 114°): n^{20}D 1.4522; ir (film) 1715 (C=O) and 1630 (conjugated C=C) cm^{-1}; nmr τ 4.85 (s, 1 H), 5.02 (s, 2 H), 5.94 (quartet, 2 H, J = 7.0 Hz), 6.58 (s, 3 H) 7.72 (s, 3 H), and 8.76 (t, 3 H, J = 7.0 Hz).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.20; H, 8.07.

Reduction of Ethyl Acetoacetate Methoxymethyl Enol Ether.—The procedure was exactly the same as that described for the reduction of 2-carbethoxycyclohexanone methoxymethyl enol ether except the ether solution was not evaporated in the work-up procedure. The crude methoxymethyl enol ether (890 mg) was reduced with 250 mg (0.036 g-atom) of lithium. After filtration

to remove the inorganic salts the ether solution was analyzed by glpc (column C, 64°, 120 ml/min) was found to contain essentially only one volatile compound. This compound was later collected by preparative glpc (column B, 73°) and was shown to be identical tc ethyl butyrate by comparison of glpc retention times and infrared spectra. The actual yield of ethyl butyrate (12) in the ether solution was determined to be 225 mg (39% from 11) by glpc (column C, 64°, 120 ml/min) using mesitylene as an internal standard. A second yield determination was made by glpc on the residual liquid (1.20 g) remaining after the ether was distilled off through a Vigreux column at atmospheric pressure. The overall yield was found to be 35%.

Reduction of Ethyl Cinnamate.—Reduction[15] of 880 mg (5.00 mmol) of ethyl cinnamate with 114 mg (0.016 g-atom) of lithium gave 983 mg of a viscous yellow liquid which contained only one volatile compound as shown by glpc (column B, 121°, 150 ml/min). This compound was found to be identical with ethyl hydrocinnamate (14) by comparison of infrared and nmr spectra. The actual yield of the ester was determined to be 18% by glpc (column B, 121°, 150 ml/min) using ethyl phenylacetate as an internal standard. A second reduction by the same procedure except that 128 mg of lithium was used gave a 16% yield of ethyl hydrocinnamate.

Reduction of *trans*-Cinnamic Acid.—A solution of 740 mg (5.0 mmol) of *trans*-cinnamic acid in 26 ml of ether was added with stirring to a solution of 148 mg (0.021 g-atom) of lithium in 82 ml of anhydrous ammonia under argon. The solution was stirred for 15 min at the liquid ammonia boiling point and was then cooled 5 min with powdered Dry Ice before quenching with 7.5 g of ammonium chloride. After addition of 60 ml of ether and evaporation of the ammonia, the reaction mixture was acidified with 10% concentrated hydrochloric acid. The ether extract was washed with water, dried with sodium sulfate, and evaporated to give 743 mg of a viscous oil. Glpc analysis (column C, 142°, 120 ml/min) of the oil revealed that only hydrocinnamic acid was present and that the actual yield of the acid was 65%. Crystallization of the oil in petroleum ether (bp 30–60°) and recrystallization from the same solvent gave 390 mg (52%) of hydrocinnamic acid, mp 46–48° (lit.[16] mp 48°). The infrared spectrum was identical with that of authentic hydrocinnamic acid.

Registry No.—2-Carbethoxycyclohexanone methoxymethyl enol ether, 25096-42-8; 2-carbethoxycyclopentanone methoxymethyl enol ether, 25096-43-9; 2-carbethoxy-4-*t*-butylcyclohexanone methoxymethyl enol ether, 25096-44-0; ethyl benzoylacetate methoxymethyl enol ether, 25096-45-1; ethyl 2-*n*-butylacetoacetate methoxymethyl enol ether, 25095-46-2; ethyl acetoacetate methoxymethyl enol ether, 25096-47-3; *cis*-**8**, 25096-48-4; *trans*-**8**, 25096-49-5.

Acknowledgments.—We thank the National Science Foundation for support in the form of a traineeship to J. E. S. and the National Institutes of Health for financial assistance.

(16) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N.Y., 1964, p 312.

Isolation and Structure of Two New Germacranolides[1] from *Polymnia uvedalia* (L.) L.

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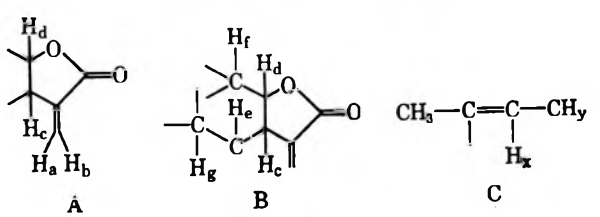
Examination of several collections of *Polymnia uvedalia* (L.) L. yielded varying quantities of two new highly oxygenated germacranolides uvedalin (**1a**) and polydalin (**1d**) which were correlated. Experiments and spectroscopic studies which led to the determination of their structure are described. *P. laevigata* Beadle gave the eudesmanolide ivalin. The flavone artemetin was isolated from *P. canadensis L.*, which contained only small amounts of sesquiterpene lactones.

As part of our general study of subtribe *Melampodiinae*, tribe *Heliantheae*, family *Compositae*,[2] we have investigated North American representatives of the genus *Polymnia* which is endemic to the Western Hemisphere.[3] The isolation and structure determination of two new highly oxygenated germacranolides from *Polymnia uvedalia* (L.) L. is reported herewith.

Collections of *P. uvedalia* from Rabun County, Ga., Leon County, Fla., and W. Va. furnished two crystalline sesquiterpene lactones whose relative yield varied somewhat with location[4] and which were named uvedalin and polydalin.

Uvedalin (**1a**), $C_{23}H_{28}O_9$, mp 131–3°, $[\alpha]D$ +12.8°, was a conjugated γ-lactone (ir bands at 1765 and 1665 cm^{-1}, with strong uv end absorption). The nmr spectrum (Table I) exhibited the typical two doublets (H_a and H_b) of partial structure A whose presence was confirmed by facile formation of a pyrazoline (**2a**) and by controlled sodium borohydride reduction to a dihydro derivative **3a** in whose nmr spectrum the signals of H_a and H_b were replaced by a new methyl doublet. Spin-decoupling experiments involving H_a and H_b established the location of the H_c multiplet at 2.8 ppm; this in turn was coupled to two doublets of doublets at 5.00 and 6.55 ppm, one of which represented the H_d resonance.

The other doublet of doublets was tentatively assigned to hydrogen (H_e) under one of three ester functions whose presence was indicated by the consump-



(1) Supported in part by grants from the National Science Foundation (GB-6413) and the U. S. Public Health Service (RG-05814).

(2) The original impetus for these studies is given by W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 1110 (1970).

(3) The most recent review of this genus is by J. R. Wells, *Brittonia*, **17**, 144 (1965).

(4) Although the three previously described[5,6] varieties of *P. uvedalia* are no longer recognized,[6] the variation in lactone content might be due to the existence of separate chemical races. Material from both West Virginia and Georgia would have keyed out as var. *uvedalia* although differing consistently in lactone content, while material from Florida, which chemically resembled the collection from Georgia, would have been assigned to var. *floridana*.[5] This problem is receiving further attention from Dr. J. R. Wells.

(5) S. F. Blake, *Rhodora*, **19**, 46 (1917).

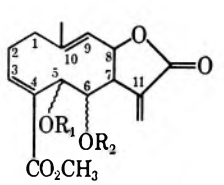
(6) J. R. Wells, *ibid.*, **71**, 786 (1969). We are indebted to Dr. Wells for authenticating the collections and for valuable correspondence.

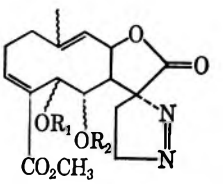
TABLE I

NMR SPECTRA OF UVEDALIN, POLYDALIN AND DERIVATIVES[a]

Compd	H-3	H-5	H-6	H-7	H-8[b]	H-9[b]	H-13	H-3′	Me C-10	Me C-2′	Me C-3′	CO_2Me	AC
1a	6.92 (m)	5.33 (d, 8.4)	6.55 (dd, 8.4, 1.4)	2.8 (m)			5.61 (d, 3) 6.12 (d, 3.5)	2.99 (q, 5.4)	1.96 (br)	1.44	1.14 (d, 5.4)	3.72	1.96
1b	6.98 (m)	5.38 (d, 8.4)	6.61 (dd, 8.4, 1.4)	2.8 (m)			5.74 (d, 3) 6.22 (d, 3.5)	4.16 (q, 6.5)	1.98 (br)	1.29	1.49 (d, 6.5)	3.80	1.98
1c	7.05 (m)	5.41 (d, 8.4)	6.64 (dd, 8.4, 1.4)	2.8 (m)	5.11 (dd)	4.93 (dd)	5.73 (d, 3) 6.27 (d, 3.5)	3.8 (q)	2.00 (br)	1.22	1.20 (d, 8.5)	3.81	2.00
1d	7.03 (m)	5.36 (d, 8.4)	6.60 (dd, 8.4, 1.4)	2.8 (m)			5.74 (d, 3) 6.26 (d, 3.5)		2.00 (br)	1.50	2.19	3.81	2.00
3a	7.01 (m)	5.39 (d, 8.4)	6.25 (dd, 8.4, 1.4)	2.8 (m)			1.26 (d,[c] 6.5)	3.08 (q, 5.4)	1.97 (br)	1.53	1.30 (d, 5.4)	3.80	1.97
3c	7.05 (m)	5.43 (d, 8.4)	6.26 (dd, 8.4, 1.4)	2.8 (m)			1.29 (d,[c] 6.6)		1.99 (br)	2.47		3.83	1.99
3d	6.81 (m)	3.85 (d, 8.0)	4.37 (d, br 8.0)	2.6 (m)	5.03 (dd)	4.74 (d, br)	1.15 (d,[c] 7.0)		1.83 (d, 1.0)			3.73	
3e	7.00 (m)	5.36 (d, 8.4)	6.15 (dd, 8.4, 1.4)	2.7 (m)	4.95 (dd, 8.5, 10.3)	4.77 (d, br, 10.3)	1.27 (d,[c] 6.5)					3.80	2.12 1.99
3f	7.01 (m)	5.29 (d[e])	5.18 (d, br[e])	2.8 (m)	4.96 (dd)	4.87 (d, br)	1.22 (d,[c] 7.0)		1.93 (d, 1.2)			3.88	2.08
3g	6.90 (m)	4.00 (d, 9)	4.86[c]	2.3 (m)			1.35 (d,[c] 5.5)		1.90 (br)	1.25[d]		3.77	
4a	6.75 (dd, 4.5, 11.5)	5.96 (d, 8.4)	6.15 (d, 8.4)		5.00 (m)		1.10 (d,[c] 6.5)	3.03 (q, 5.4)	1.00	1.46	1.27 (d, 5.4)	3.80	2.00
5a	7.14 (dd, 7.0, 10.2)	5.90 (d, 8.4)	6.73 (dd, 8.4, 1.4)	3.0 (m)	4.24 (t, br, 9.4)	2.70 (d, br, 9.4)	5.84 (3) 6.23 (d, 3.5)	3.04 (q, 5.4)	1.70	1.47	1.20 (d, 5.4)	3.74	2.06
6a	7.16 (dd, 7.0, 10.2)	5.98 (d, 8.4)	6.32 (dd, 8.4, 1.4)	2.1 (m)	4.22 (t, br, 9.4)	2.60 (d, br, 9.4)	1.30 (d,[c] 6.5)	3.08 (q, 5.4)	1.70	1.52	1.31 (d, 5.4)	3.84	2.05
7a		5.43[e]	5.43[e]		5.00 (m)		1.16 (d, 6.5)	3.05 (q, 5.4)	1.00	1.50	1.31 (d, 5.4)	3.73	2.04
8	6.87 (m)	5.20 (m)		2.8 (m)			1.35 (d, 7.0)		1.80 (d, 0.5)				
9a	7.08 (d, br)	5.00 (d, 8.4)	5.95 (dd, 8.4, 1.4)	2.7 (m)			3.08[g]	3.12 (q, 5.4)	1.94 (br)	1.54	1.32 (d, 5.4)	3.80	2.04

[a] Spectra were run in $CDCl_3$ on a Varian A-60 nmr spectrometer using TMS as internal standard. Chemical shifts are in parts per million. Signals are denoted in the usual way: d, doublet; t, triplet; q, quartet; m, multiplet; c, complex signal whose center is given; br, somewhat broadened singlet. Unmarked signals are singlets. Figures in parentheses are line separations in hertz. Signals in first eight columns correspond to one proton unless otherwise specified; signals in last five columns correspond to three protons. [b] Generally the overlapping AB part of ABX system centered in the region of 4.9–5 ppm, with H_A (α H-8) at lower field and H_B (H-9) at higher field. For chemical shifts and coupling constants in case of 1a, see Table II. [c] Three protons. [d] Two methyls of acetonide. [e] Superimposed signals. [f] AB system centered near 5.4 ppm. [g] Two protons.





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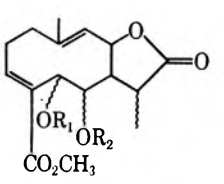

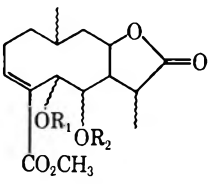

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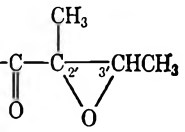
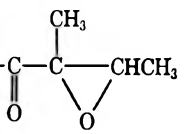
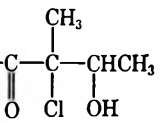
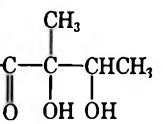
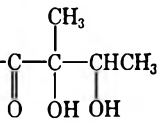
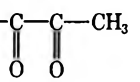
1a, R_1 = Ac; R_2 = 

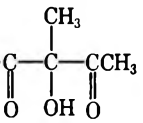
3a, R_1 = Ac; R_2 = 

b, R_1 = Ac; R_2 = 

b, R_1 = Ac; R_2 = 

c, R_1 = Ac; R_2 = 

c, R_1 = Ac; R_2 = 

d, R_1 = Ac; R_2 = 

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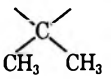
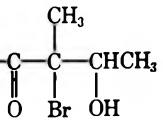
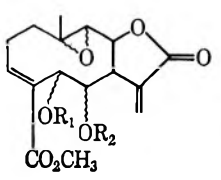
g, R_1, R_2 = 

e, R_1 = Ac; R_2 = 

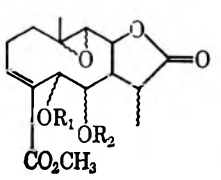
tion of 3.9 equiv of alkali on hydrolysis and by ir bands at 1740, 1725, and 1710 cm^{-1}. The multiplicity of H_d and H_e permitted further expansion to B.

The presence, in the nmr spectra of uvedalin and all of its derivatives, of a sharp three-proton singlet near 2 ppm suggested that one of the ester groups was an acetate.[7] A second ester function was probably associated with a carbomethoxy group (three-proton signal near 3.8 ppm which disappeared on basic hydrolysis). Lastly, if uvedalin were a sesquiterpene lactone as seemed likely, its empirical formula required a five-carbon acid as the third ester component.

Catalytic hydrogenation of **1a** with Pd–C yielded tetrahydrouvedalin (**4a**). The transformation of **1a** to **4a** involved, in addition to reduction of the exocyclic methylene group, saturation of the system C (ir band at 1675 cm^{-1}) as evidenced by disappearance from the nmr spectrum of a narrowly split vinyl methyl resonance and its replacement by a new methyl doublet. The vinyl proton associated with this system (H_x) had its signal at 4.85 ppm, broadened by coupling to the vinyl methyl group and coupled in turn (ABX system) to some other proton (H_y). Further evidence for C was the conversion of **1a** and **3a** to epoxides **5a** and **6a**.



5a



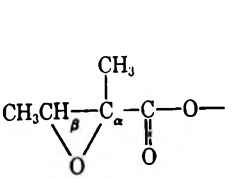
6a

In the nmr spectra of these substances the methyl signal appeared as a sharp singlet and the resonance of the vinyl proton (H_x) had moved upfield to near 2.7 ppm.

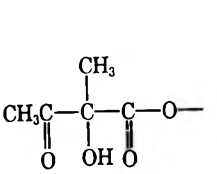
(7) A negative iodoform test ruled out the possibility that this was a methyl ketone signal.

Treatment of uvedalin with hydrochloric acid in dioxane resulted in addition of the elements of hydrogen chloride. In the nmr spectrum the conversion of **1a** to the product **1b** was attended by the shift of a one-proton quartet from 2.99 to 4.16, the shift of a methyl doublet from 1.14 to 1.49, the shift of a methyl singlet from 1.44 to 1.29, and the appearance of an –OH resonance at 3.27 ppm (disappears on deuterium exchange, ir band at 3525 cm^{-1}). That the new hydroxyl group was tertiary was indicated by the nmr spectrum and the failure of **1b** to undergo oxidation with Jones reagent. These observations could be accommodated by assuming the presence of D as the five-carbon ester side chain. This was conclusively established by hydrolysis experiments to be described subsequently and by double resonance experiments which showed that the methyl doublet at 1.14 ppm (H_γ) was coupled to the quartet at 2.99 ppm (H_β).

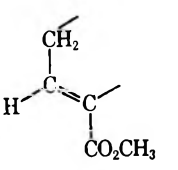
Uvedalin on treatment with sulfuric acid in aqueous acetone gave a diol **1c**. Jones oxidation of this substance followed by separation of two isomers gave pure **1d**, identical in all respects with natural polydalin $C_{23}H_{28}O_{10}$, mp 181–183°, $[\alpha]D$ +8.4°. The spectral changes were consonant with the conclusion that polydalin differed from uvedalin only in containing the side chain E instead of D.



D



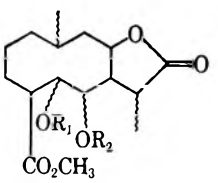
E



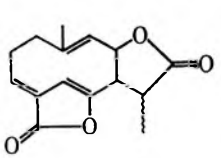
F

The foregoing evidence in favor of partial structures A, C, and D and the presence of an acetate function accounted for seven of the nine oxygen atoms present in

1a. Since the uv spectra of 3a and 4a still showed strong end absorption, thus indicating the presence in uvedalin of a second chromophore (ir bands in 1a at 1710 and 1625, in 3a at 1720 and 1630, in 4a at 1720 and 1645 cm^{-1}), it was deduced that the carbomethoxy group which accounted for the remaining two oxygen atoms was conjugated and associated with the signal of a low field proton near 7 ppm whose chemical shift required it to be vinylic and attached to the β position. In support of this hypothesis, hydrogenation of 1a with platinum oxide furnished a hexahydro derivative 7a



7a



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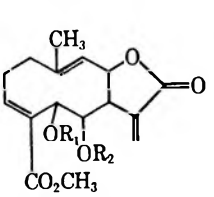
which was transparent in the uv. The conversion of 1a to 7a was accompanied by disappearance of the 7-ppm signal in the nmr, the disappearance of the remaining double-bond frequency, and the shift of the 1710 band to 1740 cm^{-1} in the ir.

Spin-decoupling experiments at 90 MHz[8] eventually permitted expansion of partial structure B to G. Irradiation at the frequency of H-6 (H_e of B) affected the signal of H-7 (H_c) and collapsed the doublet of H-5 (H_f or H_g) at 5.4 ppm to a sharp singlet. Conversely, irradiation at the frequency of H-5 collapsed the H-6 resonance but indicated no observable allylic coupling of H-5 to the low field vinyl signal near 7 ppm (H-3). Irradiation of H-3 affected signals in the methylene region, hence the grouping F was present.

Since the signals of H-8 (H_d) and H-9 (H_f or H_g) overlapped in the nmr spectrum of 1a the 90 MHz nmr spectrum of 6a was studied. Irradiation of the H-7 multiplet (H_c) at 2.1 ppm collapsed a doublet of doublets at 6.3 (H-6 = H_e) to a doublet and converted the triplet of H-8 at 4.14 ppm (H_d) to a doublet. In turn, irradiation of H-8 simplified the signal of H-7 and collapsed a doublet at 2.57 ppm to a singlet. Since this doublet originated in proton H_x of partial formula C (*vide supra*), H_y of C was identified as H_d of B. If it is borne in mind that H-5 (now identified as H_g of B) is only coupled to one proton, *i.e.*, H-6, and that the empirical formula requires the presence of an additional methylene group, only one combination of B, C, and the methylene group is possible, *i.e.*, that represented by G. This formula also explains the observation that H-9 of 1a is not only coupled vicinally to H-8 (J = 10.3 Hz) and allylically to the C-10 methyl group ($J \sim 0.6$ Hz), but that there exists another allylic coupling (J = 0.8 Hz) to one of the protons on C-1.



G

(8) We are grateful to the National Science Foundation for a grant which permitted purchase of a Bruker 90-MHz nmr spectrometer.

The problem of assigning the acetate and α-methyl-α,β-epoxybutyrate groups to C-5 and C-6 remained and was solved in the following manner. After attempts at selective hydrolysis of 1a, 1d, 4a, or 5a had resulted in complex mixtures or remained unsuccessful, it was reasoned that in accord with previous experience[9] selective hydrolysis of a pyruvate function in the presence of an acetate might be achieved. Hence, tetrahydropolydalin (3b)[10] was converted by periodate oxidation to the pyruvate 3c which had relevant nmr signals at 5.43 (d, H-5) and 6.26 (dd, H-6).

Treatment of 3c with potassium carbonate at room temperature for 2.5 hr effected complete hydrolysis to the diol 3d (H-5 signal at 3.85, H-6 signal at 4.37 ppm) which gave a positive periodate test for the presence of a vicinal glycol function and was further characterized as the diacetate 3e (H-5 signal at 5.36, H-6 signal at 6.15 ppm). However, when exposure of 3c to sodium bicarbonate was limited to 15 min, selective hydrolysis occurred with formation of the monoacetate 3f. In the nmr spectrum of this substance the signals of H-5 and H-6 were superimposed near 5.3 ppm which clearly demonstrated that hydrogen on carbon carrying the acetate function of uvedalin or polydalin was responsible for the doublet near 5.3 ppm and identical with H-5. Hence the gross structures of uvedalin and polydalin were those shown in formulas 1a and 1d.

Hydrolysis of 3c by refluxing methanolic potassium carbonate for 3 hr followed by acidification resulted in a dilactone whose formulation as 8 was in keeping with the spectroscopic evidence [uv maximum at 249 nm; ir bands at 1778, 1760, 1655, and 1650 (sh); for nmr spectrum see Table I]. Its formation established the presence of a carbomethoxy group chemically and proved that its location was γ to the oxygen function on C-6.

As concerns stereochemistry, it is assumed that the absolute configuration of the C-11 side chain is β as in all other sesquiterpene lactones of established stereochemistry. An attempt to distinguish between *cis* and *trans* stereochemistry of the 9,10 double bond on the basis NOE's was not satisfactory.[11] Moreover, although it was possible to convert 3d to an acetonide 3g, inspection of molecular models showed that this information and knowledge of coupling constants obtained by inspection of Table I and from spin-decoupling experiments was not sufficient to determine the stereochemistry at C-5 and C-6.[14]

On the other hand, the strongly negative Cotton effect exhibited by 1a (λ_{max} 225 nm, θ −1810) suggested *cis* fusion of the γ-lactone ring, if a recently formulated empirical rule relating to the sign of the lactone Cotton effect to the nature of the lactone ring

(9) W. Herz and M. V. Lakshmikantham, *Tetrahedron*, 1711 (1965).

(10) Treatment of 1d with sodium borohydride reduced not only the exocyclic double bond conjugated with the lactone, but also the keto group of the side chain. The resulting gummy material was apparently a mixture of C-3′ epimers (nmr spectrum).

(11) Although NOE's involving H-9 or H-1 and the C-10 methyl group have been used successfully for this purpose,[12,13] no useful results could be obtained in the present instance, apparently due to sample difficulties.

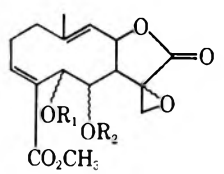
(12) W. Herz, P. S. Subramaniam, P. S. Santhanam, K. Aota, and A. L. Hall, *J. Org. Chem.*, **35**, 1453 (1970).

(13) K. Takeda, I. Horibe, M. Teraoka, and H. Minato, *Chem. Commun.*, 940 (1968); *J. Chem. Soc. C*, 1491 (1969).

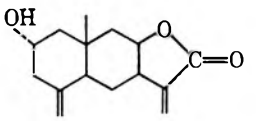
(14) Unfortunately it was not possible to determine unambiguously $J_{6,7}$ in 3g which might have aided in establishing the relative stereochemistry at these centers.

junction[15] were applicable. From the molecular model of uvedalin with H-8 α formation of a pyrazoline would then be predicted to occur predominantly by attack of diazomethane from the α side, regardless of the configuration at C-5 or C-6. The resulting pyrazoline **2a** would be expected to display a curve of negative sign.[16] This was indeed observed (λ_{max} 316 nm, θ −4900).

Polymnia laevigata Beadle furnished considerable quantities of ivalin (**10**), a eudesmanolide previously



9a



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isolated only from certain *Iva* species.[17,18] *Polymnia canadensis L.* contained a small amount of a sesquiterpene lactone mixture; the only substance isolated in crystalline form was artemetin (5-hydroxy-3,4′,5′,6,7-pentamethoxyflavone).[19] The implications of these findings will be discussed elsewhere.

Experimental Section[20]

Extraction of *Polymnia uwedalia*. (**A**).—Dried and ground leaves of *Polymnia uwedalia* (L.) L., wt 4.5 kg, collected by Dr. J. R. Wells on Aug 26, 1966, in Calhoun Co., W. Va., 3.1 miles from the Gilmer-Calhoun Co. line (voucher specimen on deposit in herbarium of the Cranbrook Institute of Science, Bloomfield Hills, Mich.) was extracted with chloroform and worked up in the usual manner.[16] The crude gum, wt 34 g, was chromatographed over 1.1 kg of silicic acid (Mallinckrodt, 100 mesh), 1000-ml fractions being collected in the following order: 1–6 (benzene), 7–18 (benzene–chloroform, 4:1), 19–32 (benzene–chloroform, 1:1), 33–52 (benzene–chloroform, 1:4), 53–62 (chloroform), 63–71 (chloroform–ether, 19:1), 72–77 (chloroform–methanol, 19:1), 78–80 (chloroform–methanol, 9:1). Fractions 23–32 eluted a gum which showed a major spot on tlc. Rechromatography over 300 g of silicic acid gave 8.0 g of crude uvedalin on elution with benzene–chloroform (1:1) which on recrystallization from ethyl acetate–hexane gave 4.5 g of pure material. Fractions 50–55 gave a gum showing a major spot. Rechromatography over 100 g of silicic acid gave 1.58 g of crude polydalin in the chloroform fractions. Recrystallization from ethyl acetate gave 0.6 g of pure material. Fractions 59–71 eluted a gum which showed two major overlapping spots on tlc. The lactones responsible for the spots could not be separated satisfactorily and polymerized rapidly. All other fractions gave gums showing several spots. Repetition of the extraction with *P. uwedalia* collected at the same spot on Aug 1, 1969, gave approximately the same results.

(**B**).—Ground *P. uwedalia*, collected by Mr. R. Lazor on July 12, 1969, in Leon County, Fla. (Lazor No. 3744 on deposit in herbarium of Florida State University), wt 10.9 kg, was extracted in the usual manner. The crude gum, wt 35 g, was chromatographed over 1 kg of silicic acid, 800-ml fractions being collected in the following order: 1–10 (benzene), 11–20 (benzene–chloroform 2:1), 21–30 (benzene–chloroform 1:2), 31–50 (chloroform), 51–60 (chloroform–methanol 19:1), 61–74 (chloroform–methanol 9:1). Fractions 21–24 contained several spots one of which corresponded to uvedalin. Fractions 32–35 eluted semicrystalline material which yielded 2.5 g of pure polydalin. Fractions 61–63 gave a gum showing a major spot. This was recrystallized from ethanol and gave 2.1 g of a crystalline saturated alicyclic alcohol, mp 275–278°. All other fractions were gums showing several spots.

(**C**).—Extraction of 2.8 kg of *P. uwedalia*, collected by Mr. R. Lazor on Aug 11 in Rabun County, Ga. (Lazor No. 3783), in the usual manner gave 10 g of crude gum which on chromatography, as described in section B, afforded 2.5 g of crude polydalin and in the earlier fractions a spot corresponding to uvedalin.

Uvedalin (**1a**): mp 131–133°; $[\alpha]^{24}D$ +12.8° (c 4.69); ir bands at 1765, 1740, 1725, 1710, 1665, and 1625 cm^{-1}; uv λ_{max} 210 nm (ϵ 14,300); CD curve (1 cm cell) λ_{max} 255 nm (θ −1810). The 90-MHz nmr spectrum and all coupling constants determined by double irradiation are listed in Table II.[21]

TABLE II

90-MHz SPECTRUM OF UVEDALIN

	Ppm	Hz
H-1a,b	2.1–2.8 (c)	$J_{1a,9} = 0.8$[a]
H-2a,b	2.1–2.8 (c)	$J_{2a,3} = 7.6, J_{2b,3} = 9.6$
H-3	6.99 (c)	
H-5	5.40 (d)	$J_{5,6} = 8.4$
H-6	6.64 (dd)	$J_{6,7} = 1.4$
H-7	2.77 (m)	$J_{7,8} = 8.4$
H-8	5.10 (dd)	$J_{8,9} = 10.3$
H-9	4.96 (dbr)	$J_{9,C\text{-}10\ Me} \sim 0.6$
C-10 Me	2.01	
$H\text{-}13_{cisoid}$	5.71 (d)	$J_{7,13\text{-}cis} = 3.1$
$H\text{-}13_{transoid}$	6.25 (d)	$J_{7,13\text{-}trans} = 3.4$
C-2′ Me	1.46	
C-3′ Me	1.19 (d)	$J_{3',3'\text{-}Me} = 5.4$
H-3′	3.01 (q)	
Acetate	2.01	

[a] Values of all coupling constants were confirmed by double irradiation or INDOR experiments.

Anal. Calcd for $C_{23}H_{28}O_9$: C, 61.60; H, 6.29; O, 32.11. Found: C, 61.36; H, 6.31; O, 32.15.

Pure polydalin (**1d**) melted at 181–183° and had $[\alpha]^{21}D$ +8.4° (c 5.36); ir bands at 1765, 1735, 1725, 1710, 1670, and 1628 cm^{-1}; uv end absorption (ϵ 27, 100 at 202 nm), CD curve (1 cm cell) λ_{max} 253, 310 nm (θ − 1740, −694); positive iodoform test.

Anal. Calcd for $C_{23}H_{28}O_{10}$: C, 59.48; H, 6.08; O, 34.45. Found: C, 59.50; H, 5.98; O, 34.97.

Reactions of 1a. (**A**).—A solution of 100 mg of **1a** in 2 ml of methanol and 2 ml of 1 *N* sodium hydroxide was heated on the water bath for 15 min, evaporated to dryness at reduced pressure and the residue titrated with 0.1 *N* hydrochloric acid. This indicated that 3.9 mol equiv of base had been consumed.

(**B**).—A solution of 100 mg of **1a** in 20 ml of ether was allowed to stand with 5 ml of ethereal diazomethane at 5° for 3 days. The pyrazoline **2a** which had separated was recrystallized from ethyl acetate: yield 95 mg, mp 166–168° dec, CD curve λ_{max} 316 nm (θ −4900).

Anal. Calcd for $C_{24}H_{30}N_2O_9$: C, 58.77; H, 6.16; N, 5.71. Found: C, 59.29; H, 6.30; N, 5.78.

Dihydrouvedalin (3a).—To a solution of 0.228 g of **1a** in 10 ml of methanol was added with stirring 0.190 g of sodium borohydride in 5 ml of methanol at 0°. Stirring was continued for 1 hr, the solution was acidified, evaporated at reduced pressure, diluted with 10 ml of water, and extracted with chloroform. The washed and dried extract was evaporated and the residue was repeatedly recrystallized from ethyl acetate–hexane. Pure **3a**: yield 0.09 g; mp 183–186°; $[\alpha]^{20}D$ −35.2° (c 2.98); ir bands 1780, 1760, 1735, 1720, 1675, and 1630 cm^{-1}; λ_{max} 206 nm (ϵ 11,300).

Anal. Calcd for $C_{23}H_{30}O_9$: C, 61.32; H, 6.71; O, 31.96. Found: C, 61.75; H, 6.26; O, 31.73.

Tetrahydrouvedalin (4a).—A solution of 0.147 g of **1a** in 25 ml of ethyl acetate was reduced at atmospheric pressure with prereduced 10% Pd–C. Hydrogen uptake ceased after absorption of 2 mol equiv of hydrogen. The product was recrystallized

(15) T. G. Waddell, W. Stöcklin, and T. Geissman, *Tetrahedron Lett.*, 1313 (1969).

(16) G. Snatzke, *Riechst, Aromen, Körperpflegem.*, **19**, 98 (1969); M. Suchy, L. Dolejs, V. Herout, F. Sorm, G. Snatzke, and J. Himmelreich, *Collect. Czech. Chem. Commun.*, **34**, 229 (1969).

(17) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

(18) W. Herz, H. Chikamatsu, N. Viswanathan, and V. Sudarsanam, *ibid.*, **32**, 682 (1967).

(19) Y. Mazur and A. Meisels, *Bull. Res. Counc. Isr.*, **5A**, 67 (1955); Z. Cekan and V. Herout, *Collect Czech. Chem. Commun.*, **21**, 79 (1956).

(20) Experimental conditions specified in ref 2 apply.

(21) Chemical shifts differed slightly from the values obtained at 60 MHz (Table I) owing to small calibration errors. The spin-decoupling experiments were carried out by Mr. A. L. Hall.

from ethyl acetate–hexane. Pure **4a**, yield 0.085 g, had mp 185–187°; ir bands at 1775, 1760, 1740, 1720, and 1645 cm^{-1}; uv λ_{max} 205 nm (ϵ 10, 100).

Anal. Calcd for $C_{23}H_{32}O_9$: C, 61.05; H, 7.13; O, 31.82. Found: C, 60.93; H, 6.95; O, 32.08.

Uvedalin Epoxide (5a).—A solution of 100 mg of **1a** in 4 ml of dry chloroform was allowed to stand with 100 mg of *m*-chloroperbenzoic acid overnight at 0°. The reaction mixture was washed in the usual fashion, dried and evaporated and the residue recrystallized from acetone–petroleum ether. The pure product, yield 54 mg, had mp 218–220°; ir bands at 1765, 1755, 1732, 1715, 1665, and 1632 cm^{-1}.

Anal. Calcd for $C_{23}H_{28}O_{10}$: C, 59.48; H, 6.08; O, 34.45. Found: C, 59.21; H, 61.31; O, 34.32.

An isomeric epoxide **9a** was prepared as follows. A mixture of 0.3 g of **1a**, 10 ml of tetrahydrofuran, 2.1 g of potassium carbonate, and 2.5 ml of water was stirred overnight. The solvents were removed *in vacuo* and 5 ml of water was added. Unreacted **1a**, wt 0.21 g, was recovered by extraction with chloroform. The aqueous layer was acidified and extracted with chloroform. The washed and dried extract was evaporated and the residue was recrystallized from ethyl acetate–hexane to yield 60 mg of **9a** which had mp 158–161° (depressed on admixture of **5a**); $[\alpha]^{24}D$ +11.5° (c 4.36); ir bands at 1795, 1755, 1740, 1720, 1670, and 1630 cm^{-1}.

Anal. Calcd for $C_{23}H_{28}O_{10}$: C, 59.48; H, 6.08; O, 34.45. Found: C, 59.12; H, 6.24; O, 34.62.

Dihydrouvedalin Epoxide (6a).—Epoxidation of 0.1 g of **3a** with *m*-chloroperbenzoic acid in the manner described in the previous section gave after recrystallization from acetone–petroleum ether, 86 mg of **6a** which had mp 213–215°, $[\alpha]^{25}D$ −73.6° (c 1.97).

Anal. Calcd for $C_{23}H_{30}O_{10}$: C, 59.22; H, 6.48. Found: C, 59.20; H, 6.38.

Preparation of 1b and 1e.—A solution of 0.33 g of **1a**, 4 ml of dioxan and 0.5 ml of dilute (1:1) HCl was kept overnight with stirring, evaporated at reduced pressure, diluted with water and extracted with chloroform. The washed and dried extracts were evaporated. The residue was purified by preparative tlc and recrystallized from ethyl acetate–hexane. There was obtained 0.23 g of **1b** which had mp 177–179°; ir bands at 3525, 1765, 1750, 1735, 1710, 1670, and 1628 cm^{-1}; uv end absorption (ϵ 22,400 at 203 nm).

Anal. Calcd for $C_{23}H_{29}O_9Cl$: C, 57.03; H, 6.32; Cl, 7.33. Found: C, 57.46; H, 6.04; Cl, 7.55.

Reaction of 0.1 g of uvedalin with 0.2 ml of dilute HBr (1:1) in the same manner gave, after recrystallization from ethyl acetate, 60 mg of **1e** which had mp 174–176°; ir bands at 3522, 1763, 1750, 1732, 1715, 1668, and 1628 cm^{-1}.

Anal. Calcd for $C_{23}H_{29}O_9Br$: C, 52.17; H, 5.48; Br, 15.10. Found: C, 52.53; H, 5.73; Br, 15.04.

Conversion of Uvedalin to Polydalin.—A solution of 0.15 g of **1a** in 5 ml of acetone and 1 ml of water containing 4 drops of concentrated sulfuric acid was kept at room temperature for 24 hr, evaporated at reduced pressure and extracted with chloroform. The washed and dried extract was evaporated and the residue was chromatographed over silica gel to give 0.12 g of starting material and 0.03 g of **1c** as a gum which had ir bands at 3540 (broad), 1765, 1745, 1735, 1718, 1670, and 1628 cm^{-1}.

A solution of 0.02 g of **1c** in 4 ml of acetone and a few drops of Jones reagent was stirred for 0.5 hr at 0°. Excess reagent was destroyed by addition of methanol and the solvents were removed *in vacuo*. The residue was extracted with chloroform. The washed and dried extract was evaporated and the residue (two spots on tlc) was subjected to preparative tlc. The more polar fraction was recrystallized from ethyl acetate–hexane to give 8 mg of material, mp 180–182°, identical in all respects (mixture melting point, ir, and nmr) with naturally occurring polydalin (**1d**).

Anal. Calcd for $C_{23}H_{28}O_{10}$: C, 59.48; H, 6.08; O, 34.45. Found: C, 59.30; H, 6.02; O, 34.59.

Hexahydrouvedalin (7a).—A solution of 0.403 g of **1a** in 25 ml of acetic acid was reduced overnight at atmospheric pressure with prereduced platinum oxide catalyst until hydrogen absorption ceased (2.9 mol equiv). The product, wt 0.40 g, was a gum which could not be crystallized and had $[\alpha]^{25}D$ +15.0° (c 5.0); ir bands at 1775, 1760, and 1740 cm^{-1}; weak uv end absorption (ϵ 360 at 203 nm).

Tetrahydropolydalin (3b).—A solution of 0.386 g of **1d** in 25 ml of methanol was reduced with 0.354 g of sodium borohydride in the manner described earlier for **1a**. The product, purified by preparative tlc, was a gum which could not be crystallized and had ir bands at 3520, 1772, 1732, 1715, 1670, and 1630 cm^{-1}.

Preparation of 3c.—A mixture of 0.51 g of **3b**, 20 ml of methanol, 10 ml of water and 0.319 g of sodium metaperiodate was stirred at room temperature for 4.5 hr, evaporated *in vacuo*, diluted with water and extracted with chloroform. The washed and dried extract was evaporated and the residue was recrystallized three times from ethyl acetate–hexane to give 0.21 g of pure **3c**: mp 195–197°; $[\alpha]^{23}D$ −41.7 (c 1.2); ir bands at 1770, 1765, 1740, 1720, 1672, and 1630 cm^{-1}; uv λ_{max} 220 nm (ϵ 9100), end absorption ϵ 16, 600 at 200 nm.

Anal. Calcd for $C_{21}H_{26}O_9$: C, 59.71; H, 6.20; O, 34.09. Found: C, 60.12; H, 6.01; O, 33.80.

Hydrolysis of 3c. (A).—A solution of 0.03 g of **3c** and 0.03 g of $NaHCO_3$ in 10 ml of 80% aqueous methanol was stirred in a nitrogen atmosphere for 15 min, acidified, evaporated *in vacuo*, diluted with 5 ml of water and extracted with chloroform. The washed and dried extract was evaporated and the residue purified by preparative tlc. The product **3f**, wt 0.0287, was a gum which cound not be crystallized and had ir bands at 3400, 1765, 1730, 1710, 1670, and 1622 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86; O, 31.78. Found: C, 60.97; H, 7.15; O, 31.74.

(B).—Repetition of the above experiment with 0.15 g of **3c** and 0.15 g of potassium carbonate for 2.5 hr gave, after the usual work-up, a solid which was recrystallized from ethyl acetate–hexane. The product **3d**, wt 76 mg, had mp 168–170°; ir bands at 3520, 3360, 1765, 1690, 1670, and 1628 cm^{-1}; uv λ_{max} (220 nm) (ϵ 7100) and end absorption (ϵ 14, 400 at 202 nm).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15; O, 30.93. Found: C, 62.35; H, 6.88; O, 30.91.

Acetylation of 50 mg of **3d** in the usual fashion (acetic anhydride pyridine) and recrystallization of the product from ethyl acetate–hexane furnished 45 mg of diacetate **3e**: mp 204–206°; $[\alpha]^{24}D$ −40.6°; ir bands at 1775, 1745, 1735, 1720, 1670, and 1630 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64; O, 32.45. Found: C, 60.68; H, 6.55; O, 32.69.

The acetonide **3g** was prepared from **3d** by the anhydrous cupric sulfate–acetone method and had mp 176–178° after recrystallization from ethyl acetate (end absorption ϵ 20,000 at 203 nm). It was not analyzed, but the nmr spectrum (Table I) verified its structure.

(C).—The previous experiment was repeated by refluxing 0.03 g of **3c** and 0.03 g of potassium carbonate in 10 ml of aqueous methanol for 3 hr. After acidification, the usual work-up gave a residue which was recrystallized from ethyl acetate to give **8**: mp 246–248°; ir bands at 1778, 1760, 1655, and 1650 cm^{-1}; uv λ_{max} 249 nm (ϵ 6200) and end absorption (ϵ 2000 at 201 nm).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.22; O, 24.59. Found: C, 69.38; H, 6.59; O, 24.45.

Extraction of *Polymnia laevigata*.—Dried and ground leaves of *P. laevigata* Beadle, wt 3.6 kg, collected by Dr. J. R. Wells on July 1, 1967, 2 miles southeast of Monteagle, Tenn., and in July 1966 3.5 miles southeast of Monteagle (voucher on deposit in Cranbrook Institute of Science), were extracted with chloroform in the usual fashion. The crude gum, wt 36 g, was chromatographed over 350 g of silicic acid, 1000-ml fractions being collected in the following order: fractions 1–30 benzene, 31–45 benzene–chloroform (1:1), 46–64 chloroform, 65–70 chloroform–ether (9:1), 71–76 chloroform–methanol (9:1), 77–79 chloroform–methanol (1:1). Fractions 38–54 gave 15 g of solid which was recrystallized from ethyl acetate to give 10.5 g of pure ivalin, mp 130–132°, identified by comparison with authentic material.[18] The other fractions contained gummy mixtures (tlc) which could not be separated satisfactorily by rechromatography. **1a** and **1d** were absent.

Extraction of *Polymnia canadensis*.—Dried and ground leaves of *P. canadensis* L., wt 3.3 kg, collected by Dr. J. R. Wells in Aug 1966 and July 1967 in a ravine along a limestone talus slope at the junction of Hayden Run Road and Scioto River, Franklin County, Ohio (vouchers on deposit at Cranbrook Institute of Science), was extracted in the usual fashion with chloroform. The crude gum, wt 15 g, was chromatographed over 400 g of silicic acid, 500 ml fractions being collected in the following order: fractions 1–6 benzene, 7–15 benzene–chloroform (2:1), 16–24 benzene–chloroform (1:2), 25–30 chloroform, 31–35 chloroform–methanol (19:1), 36–40 chloroform–methanol (9:1). Fractions 22–23 which were semicrystalline were recrystallized

repeatedly from ethanol to give 18 mg of pure artemetin: mp 162–163°; mol wt (by mass spectrometry) 388; nmr signals 7.22 (d) and 6.97 (d) (J = 9.2, H-6′ and H-5′ respectively), 7.70 (H-2′), 6.48 (H-8), 3.96, 3.94, 3.92, and 3.88 ppm (4 methoxyls); and gave the color reaction previously reported for artemetin. The mixture melting point with an authentic sample[22] was not depressed. The methyl ether had mp 156–157°, mixture melting point with an authentic sample[22] undepressed. All other fractions were gums showing several spots. Repetition of the extraction with plant material collected in July 1969 at the same location gave the same results.

(22) W. Herz, *J. Org. Chem.*, **26**, 3014 (1961).

Registry No.—**1a**, 24694-79-9; **1b**, 24694-80-2; **1c**, 24694-81-3; **1d**, 24728-11-8; **1e**, 24694-82-4; **2a**, 24728-12-9; **3a**, 24728-13-0; **3b**, 24806-56-2; **3c**, 24694-83-5; **3d**, 24694-84-6; **3e**, 24694-85-7; **3f**, 24694-86-8; **3g**, 24728-14-1; **4a**, 24694-87-9; **5a**, 24694-88-0; **6a**, 24694-89-1; **7a**, 24694-90-4; **8**, 24694-91-5; **9a**, 24694-92-6; artemetin, 479-90-3.

Sesquiterpene Lactones and Lactone Glycosides from *Hymenoxys* Species[1,2]

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Received February 17, 1970

A group of interesting sesquiterpene dilactones has been isolated from some *Hymenoxys* species. Floribundin (**3**) and vermeerin (**2**), the latter previously found in South African *Geigeria* species, were isolated from the southwestern U. S. stock poison *H. richardsonii* and the South American *H. anthemoides*. *H. anthemoides* also yielded anthemoidin and themoidin which are dihydro derivatives of **2** and **3**, respectively. *H. greenei* gave **3** and the dilactone greenein (**6**). Separate collections of *H. odorata* afforded either a lactone glucoside hymenoxynin (**14a**) or the pseudoguaianolide glucoside paucin (**13a**) and a lactone lactal hymenolide (**8a**) which could be correlated with hymenoxynin and floribundin. Structures, stereochemistry, and conformations for all compounds were derived by chemical methods and extensive application of nmr techniques.

As a consequence of the discovery of a group of biogenetically "abnormal" sesquiterpene lactones, the so-called pseudoguaianolides, in some *Helenium* species,[5] the genera *Helenium* and *Gaillardia*, the latter adjoining *Helenium* in the taxonomic scheme of *Compositae* (tribe *Helenieae*, subtribe *Heleniinae*), have received careful scrutiny.[6,7] In general, elaboration of pseudoguaianolides seems characteristic of these two genera, although some exceptions have been noted.[6,8]

While *Helenieae* is thought by many to be a rather artificial assemblage not deserving of tribal status,[11] certain natural subdivisions exist. For example, it is generally agreed that the genus *Hymenoxys* is closely allied to *Helenium* and *Gaillardia*. Accordingly, chemical examination of *Hymenoxys* species appeared to be of interest. Knowledge of their sesquiterpene lactone content could conceivably contribute to a better understanding of phylogenetic relationships within the group. Moreover several representatives such as *Hymenoxys odorata* DC. and *H. richardsonii* (Hook) Ckll. var. *floribunda* (pingue bitterweed) are well-known stock poisons of the American southwest;[12] it seemed possible that sesquiterpene lactones might be responsible for their activity. We have therefore embarked on a study of this genus. In the following we report the results of our initial study of four *Hymenoxys* species. Work on other species is continuing.[13]

Results

Table I lists species included in the present investigation and the crystalline sesquiterpene lactones isolated

(1) Supported in part by a grant from the U. S. Public Health Service (GM-05814).

(2) Previous paper on Sesquiterpene Lactones: W. Herz and S. V. Bhat, *J. Org. Chem.*, **35**, 2605 (1970).

(3) To whom correspondence should be addressed.

(4) On leave of absence at Florida State University, 1967–1968.

(5) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *J. Amer. Chem. Soc.*, **84**, 3857 (1962); W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *ibid.*, **85**, 19 (1963).

(6) For reviews of work through 1966, see W. Herz, "Pseudoguaianolides in *Compositae*, Recent Advances in Phytochemistry," T. J. Mabry, R. E. Alston, and V. C. Runeckles, Ed., Appleton-Century-Croft, New York, N. Y., 1968, p 220; J. Romo and A. Romo de Vivar, "The Pseudoguaianolides, Progress in the Chemistry of Natural Products," L Zechmeister, Ed. Springer Verlag, Vienna, Vol. 25, 1967, p 90.

(7) For the most recent paper on *Helenium* species, see W. Herz, P. S. Subramaniam, and N. Dennis, *J. Org. Chem.*, **34**, 2915 (1969).

(8) To these exceptions must now be added pulchellins B, C, E, and F from Western races of *G. pulchella* Foug. Recent work[9] has shown these sesquiterpene lactones to be eudesmanolides rather than pseudoguaianolides as originally supposed.[10]

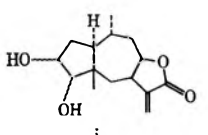
(9) H. Yoshioka, N. Dennis, W. Herz, and T. J. Mabry, *J. Org. Chem.*, **35**, 627 (1970).

(10) W. Herz and S. Inayama, *Tetrahedron*, **20**, 341 (1964); W. Herz and S. K. Roy, *Phytochemistry*, **6**, 661 (1969).

(11) A. Cronquist, *Amer. Midl. Natur.*, **53**, 478 (1955); O. Solbrig, *J. Arnoid Arboretum*, **44**, 436 (1963).

(12) J. M. Kingsbury, "Poisonous Plants of the United States and Canada," Prentice-Hall, Englewood Cliffs, N. J., 1964.

(13) While our work was in progress, two other groups reported on constituents of certain *Hymenoxys* species. Thomas and Mabry[14] isolated a number of flavonoids from *H. scaposa* DC. whereas Romo and coworkers[15] obtained a new pseudoguaianolide odoratin (**i**) from a San Luis Potosi



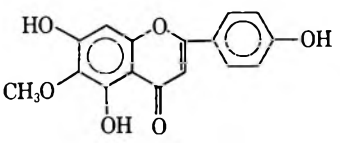
i

collection of *H. odorata*. Because we encountered different sesquiterpene lactones in collections of *H. odorata* from two separate localities (*vide infra*, Table I), the difference between the results reported by the Mexican workers and by us is not particularly surprising. Moreover, odoratin appears to be a possible precursor of the substances isolated by us (*vide infra*).

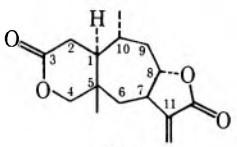
(14) M. B. Thomas and T. J. Mabry, *J. Org. Chem.*, **32**, 3254 (1967); *Tetrahedron*, 3675 (1968); *Phytochemistry*, **7**, 787 (1968).

(15) A. Ortega, A. Romo de Vivar, and J. Romo, *Can. J. Chem.*, **46**, 1538 (1968).

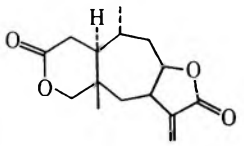
from them. In addition, the flavone hispidulin (1)[16] was found in *H. odorata* and *H. richardsonii*.



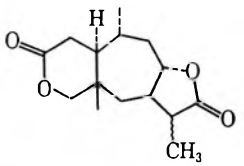
1



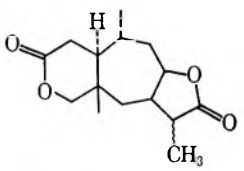
2



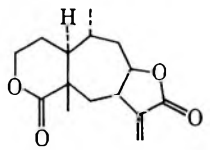
3



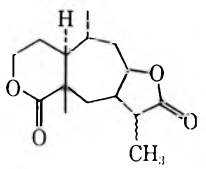
4a, methyl α
b, methyl β



5a, methyl β
b, methyl α



6



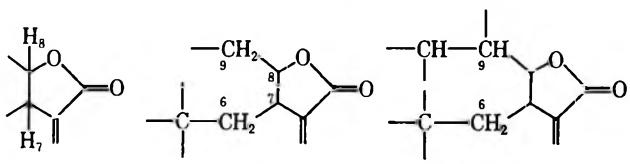
7

Vermeerin and Floribundin.—Two very similar compounds whose ir spectra indicated the presence of an α,β-unsaturated γ-lactone (1766, 1670 and 1757, 1656 cm^{-1}, respectively) and that of a δ-lactone (1729 and 1727 cm^{-1}, respectively) were isolated from *H. richardsonii*. Analysis of the nmr spectrum of the first substance (Table II) and other physical properties which will not be discussed in detail suggested that it might be identical with vermeerin, a sesquiterpene dilactone from *Geigeria aspera* Harv.[20] and *Geigeria africana* Gries[21] (*Compositae*, tribe *Inuleae*) to which formula 2 (devoid of stereochemistry) has been assigned. Direct comparison with an authentic sample of vermeerin established identity.[22]

The gross structure of floribundin[22a] shown in formula 3, stereoisomeric with that of vermeerin, was based on the detailed analysis of its nmr spectrum (Tables II and III) which immediately revealed the characteristic two doublets of the exocyclic methylene group at 6.28 (J = 2.5 Hz) and 5.60 ppm (J = 2.2 Hz). Frequency-swept decoupling experiments showed that the splitting was, as usual, caused by coupling to an allylic proton (complex multiplet at 3.21 ppm) which was in turn coupled vicinally to a proton of type –O–CH, the latter forming a symmetrical octet with degenerate central lines at 4.78 ppm (partial formula A).

Decoupling and tickling experiments showed that H-7 of A was coupled to two other protons which were responsible for two quartets in the high-field region, at 1.37 (J_1 = 15.5, J_2 = 3.5 Hz) and at 1.92 ppm (J_1 = 15.5, J_2 = 13.2 Hz). Because of the chemical shifts, these protons had to be attached to sp^3-type carbon atoms which do not carry any functional group, and because of the splitting constants, they had to be geminal.

Unambiguous assignment of the environment of H-8 of A was difficult because the distribution of signals in the high field region was unsuitable. However, the shape of the H-8 multiplet indicated the presence of couplings (3.7 and 11.7 Hz) to two protons in the remaining part of the molecule. Now it could be assumed that the larger one of these interactions (11.7) was vicinal, but the magnitude of the smaller one (3.7 Hz) does not exclude the presence of an anomalous σ–σ interaction of the type ^4J. Hence A could be extended to B or C.



A B C

The nature of the δ-lactone ring was derived by considering other features of the nmr spectrum. The low-field region contained, in addition to the signals of H-8 and H-13, a typical AB system at 4.15 and 3.83 ppm (J_{AB} = 11.0 Hz) which could be ascribed to two protons of the –O–CH type. The occurrence of this system in the floribundin spectrum can be due only to a fragment –CO–OCH_2–C– which comprises part of the six-membered lactone ring. The low-field doublet exhibited a larger line width than the high-field doublet, indicating that a further long-range coupling was present. By means of tickling experiments it was established that the long-range coupling was due to the protons of a tertiary methyl group at 1.08 ppm. Hence partial formula D could be written for the δ-lactone ring.

The nmr spectrum of floribundin contains a separate one-proton quartet at 2.84 ppm (J_1 = 5.75, J_2 = 18.75 Hz, H-2a) coupled (tickling experiments) to two other protons. One of these (H-2b) formed a quartet at 2.14 (J_1 = 11.0, J_2 = 18.75 Hz), the second (H-1) a complex

(16) W. Herz and Y. Sumi, *J. Org. Chem.*, **29**, 3438 (1964). It has been shown recently[17] that the structure previously[18] attributed to dinatin is erroneous and that dinatin is identical with hispidulin. A synthesis of hispidulin (dinatin) has been recorded.[19]

(17) D. K. Bharadwaj, S. Neelakantan, and T. R. Seshadri, *Indian J. Chem.*, **4**, 173 (1966).

(18) S. Rangaswami and E. V. Rao, *Proc. Indian Acad. Sci., Sect. A*, **54**, 51 (1961).

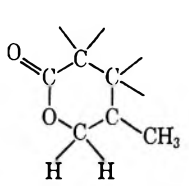
(19) P. S. Phadke, A. V. Rama Rao, and K. Venkataraman, *Indian J. Chem.*, **5**, 131 (1967).

(20) C. Rimington and G. C. S. Roets, *Onderstepoort J. Vet. Sci. Anim. Ind.*, **7**, 485 (1963).

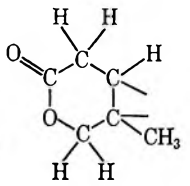
(21) L. A. P. Anderson, W. T. de Kock, K. G. R. Pachler, and C. V. D. Brink, *Tetrahedron*, **23**, 4153 (1967). We are grateful to Dr. de Kock for sending us an authentic sample.

(22) Vermeerin is the dilactone of the physiologically active vermeric acid whose occurrence in *Geigeria* species causes "vomiting disease" among sheep in South Africa.[21] The symptoms are apparently similar to those produced in livestock browsing on *H. richardsonii* in the U. S.[12] It is logical to assume that vermeerin and its congeners, or their precursors, are also responsible for the toxicity of this species.

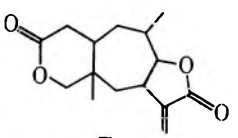
(22a) NOTE ADDED IN PROOF.—After submission of this manuscript, we learned that a compound with properties similar to those of floribundin had been isolated from *Psilostrophe cooperi* (Gray) Greene in the laboratory of Professor T. A. Geissman and assigned the same structure. This work has since been published, L. B. de Silva and T. A. Geissman, *Phytochem.*, in press. Direct comparison of floribundin and psilotropin in the laboratory of Professor T. J. Mabry established their identity.



D



E



F

multiplet hidden in the high-field region near about 1.66 ppm. The high absolute value of J_2 indicated that H-2a and H-2b were geminal protons on a sp^3-hybridized carbon bonded to a sp^2-hybridized carbon atom ($\sigma-\pi$ interaction, enhancement of geminal coupling[23]). The latter must be the carbonyl group of the δ-lactone ring. Since J_1 of H-2b also arose through coupling of H-2b to H-1, partial formula D could be expanded to E.

The only other clearly visible signal in the spectrum of floribundin was that of a secondary methyl group. Combination of B or C with E then led to two alternative formulas **3** and F which differ in the location of the secondary methyl group. The former is clearly preferred on biogenetic grounds.

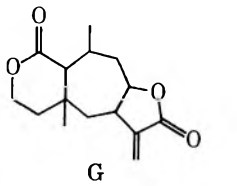
Derivation of partial formula C and therefore that of F, was based on the consideration that the smaller coupling exhibited by H-8 (3.7 Hz) might possibly be due to an anomalous long-range interaction. However, the existence of an $\sigma-\sigma$ interaction in F with a value as high as 3.7 Hz would be quite improbable. Formula F could be definitely excluded on the basis of spin decoupling experiments which showed that H-8 did not interact with the methine proton of the fragment $-CH-CH_3$. Hence floribundin possesses structure **3** (exclusive of stereochemistry).

Anthemoidin and Themoidin.—Catalytic hydrogenation of vermeerin afforded a mixture of reduction products. The major product, dihydrovermeerin A (**4a**), mp 128°, $[\alpha]$ − 25.7°, was stable to base and was also obtained in quantitative yield by sodium amalgam–acetic acid reduction of vermeerin. A minor isomer, dihydrovermeerin B (**4b**), was identical with anthemoidin. Catalytic hydrogenation or sodium amalgam reduction of floribundin gave only one crystalline dihydro derivative (**5a**) which was identical with themoidin.

Greenein.—The infrared spectrum of greenein (bands at 1770, 1735, and 1660 cm^{-1}) also suggested the presence of partial structure A and a δ-lactone group. Detailed analysis of the nmr spectrum of greenein (Tables II and III) and frequency-swept decoupling experiments showed that the constitution of greenein differed from that of **2** and **3** in the location of the fragment $-CO-O-$ of the six-membered lactone ring.

In addition to signals associated with B, the low-field region of the spectrum contained, at 4.13–4.62 ppm, signals of two protons of the type –O–CH– which had to be assigned to the fragment $-CO-O-CH_2-$. However, the appearance of this multiplet indicated that the protons of the methylene group in this fragment were coupled vicinally to at least two other protons. Hence two alternative formulae were possible, **6** (exclusive of stereochemistry) and G.

(23) L. M. Jackman and S. S. Sternbell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," 2nd ed, Pergamon Press, 1968.



G

When the spectra of floribundin and greenein are compared (Tables II and III), it becomes apparent that the chemical shifts of H-7 and H-8, as well as their vicinal and long-range couplings, are practically identical. This coincidence supports the conclusion that the configuration and conformation of ring B and the γ-lactone ring in floribundin and greenein are the same. On the other hand, H-6a and H-6b of greenein, which can be identified through their vicinal coupling constants with H-7, are considerably more deshielded, the former by 65 Hz. This deshielding effect relative to **3** can be explained in terms of formula **6**, but not in terms of G. Contrariwise, in a compound of formula G, one would expect a significant change in the chemical shifts of H-10 or of the C-10 methyl group, depending on the configuration at C-10, relative to that found in **3**, a situation which, as can be seen from Table II, does not prevail. Hence **6** is an appropriate expression for greenein.

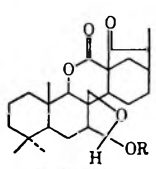
Hydrogenation of **6** afforded a dihydro derivative **7** different from **4a**, **4b**, **5a**, and **5b**. Paucity of material prevented further chemical work.

Hymenolide.—This substance **8a** had ir bands corresponding to the presence of a hydroxyl (3570, 3445 cm^{-1}) and an α,β-unsaturated γ-lactone group (1750, 1660 cm^{-1}); its nmr spectrum (see Experimental Section) exhibited signals characteristic of partial formula A, an ethoxyl group and two additional protons of type H–CO, one a singlet at 4.38 and one a doublet of doublets at 5.11 ppm.

Conversion of hymenolide to an acetate **8b**, a reaction which confirmed the presence of a hydroxyl group, was accompanied by a downfield shift of the doublet of doublets to 6.08 ppm. These unusual high paramagnetic shifts are characteristic of a hemiacetal hydrogen[24] which, because of the multiplicity of its signal, has to adjoin a methylene group.

Confirmation for the presence of such a hemiacetal linkage in hymenolide was provided by chromium trioxide–pyridine oxidation of **8a** to a dilactone **9** and by pyrolysis of **8b** to an anhydro derivative **10**. The nmr spectrum of the latter (Tables II and III) exhibited signals typical of the grouping $-CH_\gamma—CH_\beta=CH_\alpha—O-$, where H_α at 6.08, H_β at 4.70, H_γ at 2.07 ppm, $J_{\alpha,\beta}$ =

(24) Compare with the values of H-6 in the enmein derivatives iia (5.38), iib (4.72), and iic (6.15 ppm).[25]



iia, R = H
b, R = CH_3
c, R = Ac

(25) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Okamoto, M. Natsume, Y. Kawazoe, K. Sudo, T. Ikeda, M. Tomoeda, S. Kanatomo, T. Kosuge, and K. Adachi, *Tetrahedron Lett.*, 1243 (1964).

TABLE I

SESQUITERPENE LACTONES FROM *Hymenoxys* SPECIES

Species	Compd	Molecular formula	Mp, °C	$[\alpha]_D$, deg	Species	Compd	Molecular formula	Mp, °C	$[\alpha]_D$, deg
H. richardsonii (Hook)	Vermeerin[a]	$C_{15}H_{20}O_4$	145–146	−67.1	*H. greenei* (Ckll.)	Floribundin			
Ckll. var. *floribunda* (Gray) Parker	Floribundin	$C_{15}H_{20}O_4$	143	+84.0	Rydb.	Greenein	$C_{15}H_{20}O_4$	169–171	+114
H. anthemoides (Juss.) Cass.	Vermeerin[a]				*H. odorata* DC.	Hymenoxynin[b]	$C_{21}H_{34}O_9 \cdot H_2O$	125–128	−37.6
	Floribundin					Hymenolide[c]	$C_{17}H_{26}O_5$	136–138	−48.6
	Anthemoidin	$C_{15}H_{22}O_4$	220–221	−115		Paucin[c,d]	$C_{23}H_{32}O_{10}$	177–179	+64.4
	Themoidin	$C_{15}H_{22}O_4$	219–220	+61.8					

[a] Previously isolated.[20] [b] From Coahuila collection. [c] From N. M. collection. [d] Previously isolated.[28]

TABLE II

CHEMICAL SHIFTS IN NMR SPECTRA OF *Hymenoxys* LACTONES[a]

Compd	H-1	H-2a	H-2b	H-4a	H-4b	H-6a	H-6b	H-7	H-8	H-9a	H-9b	H-10	H-11	H-13a	H-13b	H-14	H-15
2	~2.06	2.70	2.35	4.11	3.87	1.84	1.46	2.79	3.99	~2.33	1.27–1.6	(~1.8)		6.16	5.45	1.02	1.09
3	~1.66 (1.63)	2.84	2.14	4.15	3.83	1.92	1.37	3.21	4.78	(~2.14)	(1.90)	(1.75)		6.28	5.60	1.09	1.08
4a		2.67	2.33	4.05	3.82				3.95			~1.70[b]	~2.22[b]	1.17		0.98	1.05
4b	1.98	2.68	2.34	4.09	3.81				4.15			~1.64[b]	~2.62[b]	1.14		0.97	1.03
5a		2.84	2.15	3.95	3.76	1.51	~1.15[c]	~2.59[c]	4.73			~1.69[b]	~2.93[b]	1.11		1.05	1.11
5b		2.81		4.06	3.79				4.77				~2.20[b]	1.32		1.06	1.07
6[d]						2.96	1.75	3.21	4.79			~1.79[b]		6.28	5.70	1.15	1.27
10[e]	2.07	...[c]		4.38		1.74	1.51	3.52[f]	4.76	1.7–2.1[c]	1.7–2.1[c]	~1.70		6.23	5.51	1.12	0.90

[a] First-order values from 100-MHz spectra (Varian HA-100), solvent $CDCl_3$, internal standard hexamethyldisiloxane (HMDS) except for **5b** and **10** (TMS). Chemical shifts given in δ (TMS) values using δ (HMDS) = 0.06 ppm. Values in parentheses are corresponding values from 220-MHz spectra (Varian HR-220). [b] From INDOR spectra. [c] Approximate value from double resonance experiment. [d] 2H 3, 4.13 4.63 ppm. [e] H-2, 4.70 ppm; H-3, 6.08 ppm; $-OCH_2CH_3$; $-CH_2-$ nonequivalent protons at 3.42–4.01 ppm, CH_3, triplet at 1.22 ppm (J = 7 Hz). [f] Hidden in the multiplet of $-CH_2-$ of ethoxyl.

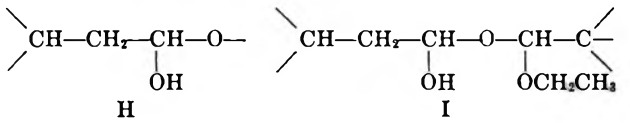
TABLE III

COUPLING CONSTANTS IN NMR SPECTRA OF *Hymenoxys* LACTONES[a]

Compd	$J_{1,2a}$[b]	$J_{1,2b}$[b]	$J_{1,10}$[c]	$J_{6a,7}$[d]	$J_{6b,7}$[d]	$J_{7,8}$	$J_{7,11}$[e]	$J_{7,13a}$	$J_{7,13b}$	$J_{8,9}$	$J_{8,9b}$	$J_{4,15}$[f]	$J_{1,15}$[f]	$J_{2a,b}$[b]	$J_{4a,b}$	$J_{6a,b}$[d]	$J_{13a,b}$[f]	$J_{11,13}$	$J_{10,14}$
2	5.6	11.5	(8.4)	2.75	11.0	9.5		3.4	3.1	4.0	11.5	0	0	17.6	11.0	15.0	0		6.1
	(5.4)	(12.6)		(2.5)	(11.4)	(10.5)				(4.0)	(10.5)			(18.3)		(15.4)			
3	5.75	11.0	(11.4)	13.25	3.5	8.0[g]		2.5	2.2	11.7[g]	3.7[g]	0	0	18.75	11.0	15.5	0		6.0
	(5.9)	(11.9)		(13.3)	(3.5)									(18.8)		(15.9)			
4a	5.8	12.0				9.2[h]	12.7			4.8[h]	10.9[h]	0		18.5	11.0			6.6	6.3
4b	5.5	12.5	7.3			10.5	7.5			5.0	10.5	0	0	17.85	11.0			7.5	6.7
5a	5.5	11.5		13.5	2.5	...[i]	8.5–9.0			...[i]	...[i]	0		18.6	11.0	15.2		7.5	6.1
5b	5.5					...[i]	...[j]			...[i]	...[i]	0		18.5	11.0			7.3	~6.0
6				3.0	13.3	8.0[g,k]		2.65	2.30	11.75[g,k]	3.75[g,k]					15.3	0		6.0
10[l]			11.5	12.0	4.5	7.8[m]		2.4	2.1	...[m]	...[m]	0[n]	0			15.0	0		6.0

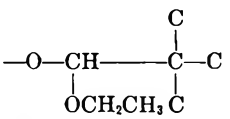
[a] First-order values from 100-MHz spectra (Varian HA-100), solvent $CDCl_3$. Values in parentheses correspond to splittings from 220-MHz spectra (Varian HR-220). Numbering of protons corresponds to that in Table II. All values taken directly from charts. [b] From multiplets of H-2a and H-2b. [c] From multiplets of H-1. [d] From multiplets of H-6a and H-6b. [e] From INDOR spectra. [f] From decoupling experiments; $J_{4,15} < 0.5$ Hz, $J_{13a,b}$ of **3** $\ll 0.5$ Hz. [g] Multiplets of H-8 identical at 100 and 200 MHz. [h] H-8 multiplet similar to that in **2**. [i] Multiplet of H-8 is virtual complex; $\Sigma \sim 23$ Hz in **5a**, ~25 Hz in **5b**. [j] Could not be estimated from INDOR spectra. [k] From multiplet of H-8 which was practically identical with that of **3**. [l] $J_{1,2} = 1.6$ Hz; $J_{1,3} = 2.65$ Hz; $J_{3,4} = 0 \ll 0.5$ Hz; $J_{2,3} = 6.35$ Hz. [m] Multiplet of H-8 coincides with H-2 multiplet; splittings 7, 8, 10.5, 5.2 Hz. [n] $W_{1/2}$ (H-15) ~ 0.8–0.9 Hz.

6.35, $J_{\alpha,\gamma}$ = 2.65, and $J_{\beta,\gamma}$ = 1.6 Hz (chemical shifts and coupling constants verified by spin decoupling).[26] Hence hymenolide contains partial formula H.



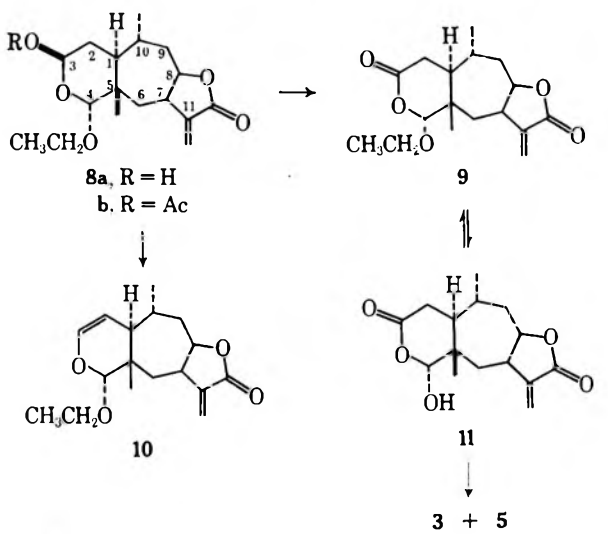
H I

Exposure of dehydrohymenolide **9** to dilute acid resulted in hydrolysis of the ethoxyl group; treatment of the product **11** with ethanolic HCl reconstituted **9**. This behavior, and the nmr spectra of **9** and **11** were consonant with the presence of the grouping



which, because of the presence of a lactone group in hymenolide and its empirical formula, must be combined with H into partial structure I. Hence, hymenolide must be **8a**, the nature of the seven-membered ring and its combination with I being established by spin-decoupling experiments on **10** (Tables II and III) in the manner described for floribundin.

Chemical evidence for the formulation of hymenolide as **8a** was provided as follows. Treatment of the lactol **11**, which is presumably in equilibrium with the aldehydo acid, with $NaBH_4$ in methanol resulted in formation of floribundin and themoidin. Hence, the configuration of hymenolide at C-1, C-5, C-7, C-8, and C-10 is the same as that of floribundin.



8a, R = H
b, R = Ac

9

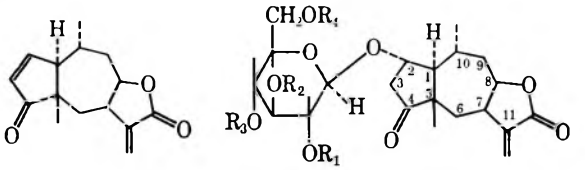
10

11

3 + 5

Paucin.—The empirical formula of a highly polar substance from the N. M. collection of *H. odorata*, its ir spectrum (strong hydroxyl absorption, α,β-unsaturated lactone at 1741 and 1668, acetate at 1729 and 1263 and cyclopentanone at 1713 cm^{-1}) and its nmr spectrum (see Experimental Section) which exhibited complex five-proton absorption characteristic of –O–CH– suggested the possibility that a glycoside of a sesquiterpene lactone had been isolated. The nmr spectrum also displayed doublets at 6.16 and 5.14 ppm (exocyclic methylene group) and, after deuterium exchange, a multiplet at 4.78 ppm characteristic of partial formula A, a methyl singlet, a deshielded methyl doublet at 1.34, an acetate singlet, and three hydroxyl protons which disappeared after deuterium exchange.

The presence of three hydroxyl groups was confirmed by conversion to a triacetate. Treatment with dilute acetic acid afforded aromatin (**12**) of known structure



12

13a, R_1 = Ac, R_2, R_3, R_4 = H
b, R_1, R_2, R_4 = H; R_3 = Ac
c, R_1, R_2, R_3 = H; R_4 = Ac
d, R_1, R_2, R_3, R_4 = Ac

and stereochemistry.[27] The facile elimination reaction and the deshielding of the C-10 methyl group suggested that the carbohydrate moiety was attached to C-2 and probably α to the sesquiterpene nucleus.

At this point a report[28] appeared on the isolation from two *Baileya* species (tribe *Helenieae*) of a sesquiterpene glucoside paucin for which formula **13a** or **13b** was proposed. The properties of paucin and our substance from *H. odorata* were sufficiently similar to warrant a direct comparison which established identity of our material with paucin.

The earlier assignment[28] of the acetyl group to C-2′ or C-4′ of the glucose moiety was based on the observation that paucin consumed only 1 mol equiv of HIO_4 when oxidized with a twofold molar excess of the reagent. However, examination of the 100-MHz spectrum of paucin revealed *three doublets* which corresponded to the three hydroxyl groups at 4.64, 4.81, and 4.95 ppm (J = 4.0, 3.8, and 4.8 Hz) because they disappeared on deuterium exchange. Formulae **13a** and **13b** would require two doublets and one triplet. Hence we prefer structure **13c** for paucin.[29] The resonance of the anomeric hydrogen was displayed as a doublet at 4.37 (J = 7.0 Hz); the large coupling constant confirmed that the glycoside moiety in paucin was β.

Hymenoxynin.—The polarity and empirical formula of the crystalline material from the Coahuila collection of *H. odorata* suggested that it, too, was a glycoside but its ir (one γ-lactone band at 1770 cm^{-1}) and nmr spectrum (Experimental Section) showed that the sesquiterpene lactone nucleus differed from that of paucin. More specifically, the presence of two methyl doublets and one methyl singlet required saturation of the exocyclic methylene group. Deuterium exchange resulted in the disappearance of four hydroxyl protons and made evident one H–CO singlet at 4.35, one H–CO doublet at 4.47 (J = 7.5 Hz),[30] one H–CO multiplet at 4.70 associated with H-8, and a plethora of signals corresponding to eight H–CO protons in the region 3.2–4.0 ppm. Acetylation to a tetraacetyl derivative confirmed the presence of four hydroxyl groups; the

(26) For a number of leading references, see W. Herz, P. S. Subramaniam, P. S. Santhanam, K. Aota, and A. L. Hall, *J. Org. Chem.*, **35**, 1453 (1970).

(27) J. Romo, P. Joseph Nathan, and F. Diaz, *Tetrahedron*, **79**, 20 (1964). We wish to thank Dr. Romo for an authentic specimen.

(28) T. G. Waddell and T. A. Geissman, *Tetrahedron Lett.*, 515 (1969). We wish to thank Professor Geissman for an authentic sample of paucin.

(29) Observation of the H-6′ resonance in the nmr spectrum of **13d** which would have resolved the ambiguity was not possible owing to overlapping of the signals.

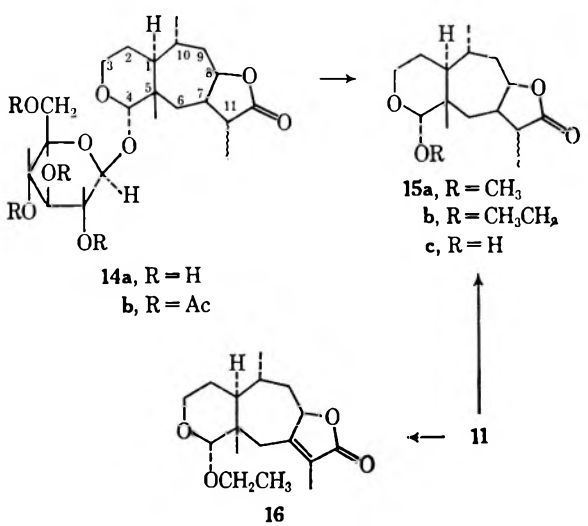
(30) Later assigned to H-4 and H-1′, respectively.

accompanying downfield shift of five protons indicated the presence of one primary hydroxyl, three secondary hydroxyls and apparently three ether hydrogens in addition to the three protons responsible for signals in the region of 4.3–4.7 ppm.

On methanolysis with concentrated hydrochloric acid at room temperature hymenoxynin afforded a methyl ether $C_{16}H_{26}O_4$ (**15a**, nmr spectrum) and glucose which was isolated as the osazone, thus establishing that hymenoxynin was an O-glucoside in which the glucose moiety was attached to the hemiacetal linkage of a sesquiterpene lactone. The nmr spectrum of **15a** had the usual H-8 H–CO multiplet at 4.77, a sharp singlet at 4.04, whose chemical shift and appearance was reminiscent of H-4 in hymenolide, and two broad signals (one proton each) at 3.70 and 2.93 ppm probably associated with CH_2O. Analogously, treatment of hymenoxynin with ethanolic hydrochloric acid afforded the ethoxy derivative **15b** and hydrolysis of hymenoxynin with hydrochloric acid in aqueous acetone yielded a lactol **15c**.

Hymenoxynin could be correlated with hymenolide in the following manner. Hydrogenation of anhydrohymenolide (**11**) with platinum oxide in ethanol afforded dihydroisoanhydrohymenolide (**16**) and a tetrahydro derivative which was identical in all respects with the hymenoxynin derivative **15b**. Since the configuration of hymenolide had been established, as will be discussed subsequently, the remaining uncertainties in the structure of hymenoxynin were the configuration at C-11 and the configuration of the C-1′ anomeric carbon atom.

In the nmr spectrum of hymenoxynin, the signal of the anomeric proton was observed at 4.47 ppm with a large coupling constant (J = 7.5 Hz) characteristic of *trans*-diaxial coupling to H-2′. Hence, the glycosidic linkage of hymenoxynin was β and hymenoxynin could be expressed as (**14a**), where the configuration at C-11 remains to be established.



Stereochemistry.—The compounds listed in Table I could not, with the exception of paucin, be correlated with other substances of known stereochemistry. As a consequence, assignment of configuration to the various asymmetric centers had to depend on more circumstantial evidence.

At the outset, it was logical to assume that the C-7 side chain, as in almost all sesquiterpene lactones of natural origin, was equatorial and β, and that H-1 was α, C-5 methyl β, and C-10 methyl α, as in all other pseudoguaianolides and modified pseudoguaianolides from *Helenium* and *Gaillardia* species. This supposition was strongly reinforced by the discovery that paucin was a derivative of aromatin (**12**) and possessed the postulated stereochemistry at C-1, C-5, C-7, and C-10. Furthermore, the gross structure of hymenolide and hymenoxynin suggested that these constituents of chemical varieties of *H. odorata* were formed by biological oxidation of odoratin,[13] a compound of known stereochemistry which had been isolated previously[15] from a different collection of *H. odorata*.[31] On this basis, vermeerin and floribundin would have structures **2** or **3** and would be C-8 epimers.

Concrete support for these expressions and evidence for the absolute configuration at C-8 was provided by a detailed analysis of the nmr spectra which will now be discussed.[32]

Vermeerin and Floribundin.—The results of our analysis (first order) of spectra obtained at 100 MHz are summarized in Tables II and III. Our analysis of vermeerin corresponds in the main to an interpretation published previously.[21] However, the South African authors incorrectly characterized the multiplets of H-1, H-2a, and H-2b as an ABX system. The 100-MHz spectrum ($CDCl_3$) displays at *ca.* 2.06 ppm a quartet which only partially represents the H-1 multiplet since H-1, being further coupled to H-10, cannot give rise to an X quartet. The distance between the outer lines of this "quartet" is about 13.5 Hz, which corresponds to the $|J_{AX} + J_{AB}|$ referred to by Anderson and coworkers.[21] In view of the relative chemical shifts of H-1, H-2a, and H-2b, and considering the coupling H-1,H-10, the quartet must be the ABC end of a larger spin system which includes H-9a and H-9b as well and cannot be analyzed exactly because of virtual coupling and because of the fact that all multiplets coincide with the multiplets due to other protons.

Line identification by means of tickling experiments showed that the lower field proton H-2a possess first-order splittings $S_{2a,2b} \cong 17.6$ and $S_{1,2a} \cong 5.6$ Hz and the higher field proton H-2b $S_{2a,2b} \cong 17.6$ and $S_{1,2b} \sim 11.5$ Hz. Comparison with the 220-MHz spectrum which provides first-order splittings $S_{2a,2b} = 18.3$, $S_{1,2a} = 5.4$, and $S_{1,2b} = 12.6$ Hz actually indicates that the system still interacts strongly at 100 MHz. These first-order splittings clearly indicate the presence of one large and one smaller vicinal interaction; assuming that both of them have the same sign, the correct coupling constants which would result from an exact analysis

(31) Unfortunately attempts to investigate the transformation of odoratin (i, footnote 13), generously supplied by Dr. Romo de Vivar, into hymenolide or one of the dihydrovermeerins or dihydrofloribundins foundered on the paucity of available starting material. Oxidation by several methods resulted in a complex mixture of products. Hymenolide which is the ethyl hemiacetal of the dialdehyde produced by glycol cleavage of odoratin is quite possibly an artefact produced from the dialdehyde or from a glycoside corresponding to **8a** by reaction with ethanol under the slightly acid conditions employed during the lead acetate precipitation stage.

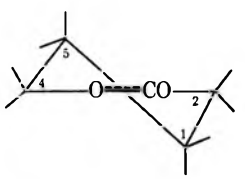
(32) The recent generalization[33] that the sign of the lactone Cotton effect of a sesquiterpene lactone which incorporates partial structure A can be used for assignment of absolute configuration is not applicable to the dilactones listed in Table I because of the superposition of two Cotton effects in the region in question.

(33) T. G. Waddell, W. Stöcklin, and T. A. Geissman, *Tetrahedron Lett.*, 1313 (1969).

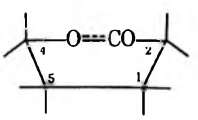
must fulfill the conditions $J_{1,2a} < S_{1,2a}$ and $J_{1,2b} > S_{1,2b}$ (high-field approximation for an ABX system). In the 220-MHz spectrum the H-1 resonance was seen as degenerate octet whose exact analysis was not possible because of virtual line broadening.[34] The approximate first-order splittings were S_1 (corresponding to $J_{1,10}$) = 8.4 Hz, S_2 (corresponding to $J_{1,2a}$) = 5.9 Hz, and S_3 (corresponding to $J_{1,2b}$) = 12.9 Hz.

In view of these and our other results, the following conclusions can be reached about the stereochemistry of vermeerin and floribundin. We will first consider the six-membered lactone ring of vermeerin and floribundin.

X-Ray and ir studies have demonstrated that the carbonyl stretching frequency of a δ-lactone in the half-chair form J lies in the range 1730–1750 and that it is higher, approximately 1758–1765 cm^{-1}, for the half-boat form K.[35] The utility of this rule has been demonstrated recently in the case of some iridolactones.[36] Since the ir spectra of vermeerin and floribundin show ν_{CO} = 1729 and 1727 cm^{-1}, respectively, it can be assumed that the δ-lactone ring of both compounds possesses the "half-chair" conformation. Support for this is found in the detailed analysis of the nmr spectra.

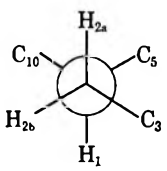


J

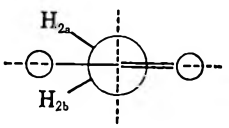


K

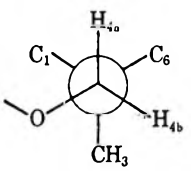
In the spectra of 2 and 3, $J_{1,2a}$ and $J_{1,2b}$ are nearly the same and chemical shifts of H-2a and H-2b are in the same order. From the magnitude of the J's it follows that the relative configuration of the fragment C-2, C-1 can be expressed approximately by the Newman projection L.



L



M



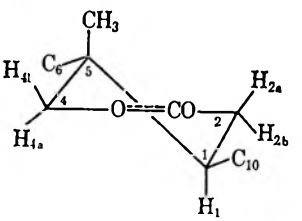
N

Both compounds exhibit a rather large geminal coupling constant $^2J_{2a,2b}$ = |18–19| Hz. Since the protons in question are attached to sp^3, not sp^2, hybridized carbon atoms, the large value must have its origin in hyperconjugative enhancement, by $\sigma-\pi$ interactions, of the order of $J^\pi \sim$ 6–7 Hz.[23,37] Such a value of J^π requires, according to theoretical calculations,[38] that a line joining H-2a and H-2b be perpendicular to the plane of the conjugated system as in M.

Moreover, in 2 and 3, one of the H-4 protons is coupled to the C-5 methyl group,[39] obviously a coupling of the W-type, which requires that the C–H and C–CH_3 bonds be antiparallel.[23] Hence the fragment C-4, C-5 can be represented approximately by projection N.

In principle, part structures L and N could be accommodated in the half-chair or the half-boat form, but the requirement for hyperconjugative interaction imposed by M is realized in the half-chair form only. In the half-boat form the dihedral angles which the H–C-2 bonds make with the plane of the conjugated CO–O system would not be equal as required by M but would differ considerably from each other, the pseudoequatorial bond lying approximately in the plane. Measurements of the solvent effect (Table IV) further demonstrate that there is little difference in the position of H-2a and H-2b with respect to the plane of the δ-lactone group since values of the solvent shift $\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$ for H-2a and H-2b are practically identical. Moreover, there is no significant difference between the Δ values for H-2 and H-4 of vermeerin on the one hand and floribundin on the other. This indicates that vermeerin and floribundin form collision complexes with approximately the same geometry.

These observations clearly support the conclusion that the δ-lactone ring is in the half-chair conformation and that the configuration of asymmetric centers C-1 and C-5 is the same in both compounds. Combination of these requirements with L and N leads to expression O for the δ-lactone ring in which H-1 and C-5 methyl are *trans*.[40]



O

We now proceed to consider the stereochemistry of the γ-lactone ring. A solution to this problem could be based, in principle, on the magnitude of the vicinal interaction of the bridgehead protons, although it is possible to distinguish unequivocally between *cis* and *trans* fusion only when conformational rigidity imposes characteristic differences of dihedral angles approximately in the sense of formulas P and Q[42] which are shown below.

(34) H-1 is part of a relatively strongly interacting system involving H-2a, H-2b, H-1, H-10, H-9a, and H-9b,; hence the multiplet couln include combination lines or wings, and the existence of true $\sigma-\sigma$ long range interactions could not be excluded.

(35) K. K. Cheung, K. H. Overton, and G. A. Sim, *Chem. Commun.*, 634 (1965).

(36) K. Sisido, K. Inomata, T. Kageyama, and K. Utimoto, *J. Org. Chem.*, **33**, 3149 (1968).

(37) Methane, J = |12.4| Hz, serves as reference.

(38) VB method, M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1899 (1963); MO method, J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, **42**, 1339 (1965).

(39) The low-field doublet of H-4a had a 1 Hz larger line width than the high-field doublet of H-4b; the presence of long-range coupling to the methyl group was established by tickling experiments.

(40) Unfortunately, it was not possible to deduce the relative configuration of H-1 and C-5 methyl directly from the nmr spectrum. The presence of $^4J_{1,15}$ which might have served to confirm the *trans* relationship could not be established. However, absence of long-range coupling of this type is not a sufficient criterion for deciding against a *trans*-ring fusion since a ^4J interaction of the angular type can be significantly influenced by the conformation of the molecule as a whole.[41]

(41) N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Amer. Chem. Soc.*, **87**, 302 (1965).

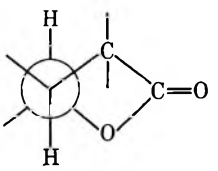
(42) J. T. Pinhey and S. Sternhell, *Aust. J. Chem.*, **18**, 543 (1965).

TABLE IV

SOLVENT SHIFTS OF VERMEERIN AND FLORIBUNDIN[a]

	H-2a	H-2b	H-4a	H-4b	H-7	H-8	H-14	H-15	H-13a	H-13b
2	0.50	0.52	0.75	0.67	0.89	0.84	0.66	0.70	0.12	0.65
3	0.50	0.56	0.73	0.63	0.90	0.70	0.64	0.65	0.11	0.61

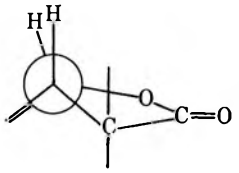
[a] Shifts expressed in $\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$; values are based on centers of multiplets; measured on Varian HA-100 using hexamethyldisiloxane as internal standard.



trans

$^3J_{H,H} > 10$ Hz

P



cis

$^3J_{H,H} \leq 8$–9 Hz

Q

This situation usually exists in the case of those systems where a γ-lactone ring is fused onto a six-membered ring. When, however, the γ-lactone is attached to a ring containing more than six carbon atoms, greater flexibility can be expected, and the difference in coupling constants may not be particularly significant.[43]

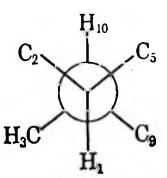
Table III indicates that the $J_{7,8}$'s in vermeerin and floribundin are not sufficiently different to warrant immediate application of the above rule. Nevertheless, comparative studies on a large group of analogous γ-lactones with well-defined stereochemistry, the detailed discussion of which will be published elsewhere,[44] have shown that the rule $0 < S_{7,8}$ (*cis*) < 8–$9 < S_{7,8}$ (*trans*) for the first-order values of $J_{7,8}$ appears to be generally applicable, especially if both isomers are available for comparison. Therefore, we assume that the fusion of the γ-lactone ring in vermeerin is *trans* and in floribundin *cis*.

This assumption is further supported by considering the magnitude of the allylic couplings of H-13a and H-13b with H-7. It has been found, by analyzing a large number of naturally occurring sesquiterpene lactones of well-defined stereochemistry containing six-, seven-, and ten-membered rings, that $^4J_{cis} \leq 3$ and $^4J_{trans} \geq 3$ Hz.[45] The application of this rule to the case at hand (Table II) again suggests that vermeerin is the *trans*- and floribundin the *cis*-fused isomer.

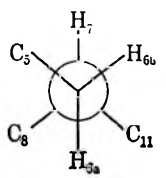
With a knowledge of the stereochemistry of the two lactone rings in vermeerin and floribundin, it should be possible in principle to establish the relative configuration of all asymmetric centers, using Dreiding models and the data of Tables II and III. However, models do not necessarily reflect the actual geometry of the molecules in question.[46] Secondly, the data obtained from first-order analysis of the nmr spectra do not always represent the true coupling constants and are incomplete with respect to the vicinal couplings H-9, H-10 which could not be estimated owing to superposition of signals. In solving the conformational problem of the seven-membered ring, the following additional data are of importance.

(1) Coupling $J_{1,10}$: The magnitude of $J_{1,10}$ determines the relative configuration at C-1,C-10; hence, if the configuration of H-1 is established, the configuration at C-10 is known. In the case of floribundin, $J_{1,10} = 11.4$ Hz and the diaxial relationship of H-1 and H-10 shown in R can be deduced. In the case of vermeerin, $J_{1,10} = 8.4$ Hz, a value which unfortunately does not permit an unequivocal decision as to the nature of the H-1,H-10 relationship, although it seems highly unlikely that the stereochemistry at C-10 is different from that in floribundin.

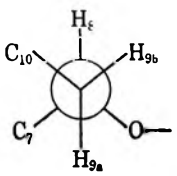
(2) Couplings $J_{6,7}$ and $J_{8,9}$: Table III clearly indicates the presence of one diaxial coupling around the bonds C-6,C-7 and C-8,C-9 of both compounds, as illustrated in S and T.[48]



R



S



T

If we assume a half-chair conformation for the δ-lactone ring and a *trans* fusion of the δ-lactone with the seven-membered ring (O) as deduced previously, a limited number of possible arrangements containing a *cis*- or *trans*-γ-lactone-ring fusion exists. These are summarized in Table V.

Let us consider first the floribundin molecule. Two formulas, **3** and **3a**, which express the relative stereochemistry, can be written for each of which there exists only one suitable conformation. In the case of **3**, this is the conformation containing the C_1[49] (or C_6) boat form of the seven-membered ring; in the case of **3a**, it is the C_1 chair form. Both conformations are in accord with the data presented up to this point. A distinction between the two would be possible if the vicinal couplings around the C-9,C-10 bond could be estimated. The C_1 boat form of **3** would be preferred if one assumes that repulsion due to the C-5 methyl group exerts a dominant influence. Its model indicates that it contains only two 1,3-diaxial interactions, $CH_3 \longleftrightarrow$ H-2a and $CH_3 \longleftrightarrow$ H-10, whereas the C_1 chair of **3b** also contains the repulsion $CH_3 \longleftrightarrow$ H-7. On the other hand, the C_1 chair form of **3a** contains only one transannular H–H interaction of importance, H-9 (*endo*) $\longleftrightarrow$ H-6 (*endo*),

(43) For example, in compounds of the santonin series, $^3J_{trans} = 11$–12 and $^3J_{cis} = 8$ Hz. On the other hand, in isophotosantoinic acid lactone (*trans*), $J_{6,7} = 9.0$ Hz, and, in 6-epiisophotosantonic acid lactone (*cis*), $J_{6,7} = 7.8$ Hz.[42]

(44) Z. Samek, in preparation. Because first-order values can be used only within certain ranges of $|J/\Delta\nu|$, it may be necessary to vary internal shifts by means of solvent effects or by change of external field.

(45) Z. Samek, *Tetrahedron Lett.*, 671 (1970).

(46) For example, in the case of bromohelenalin, significant differences between the structure determined by X-ray analysis[47] and the model were found.

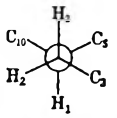
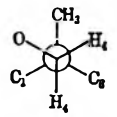
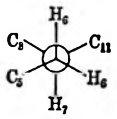
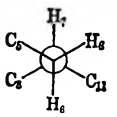
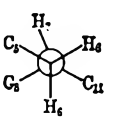
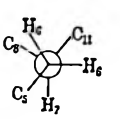
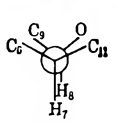
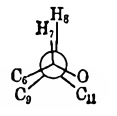
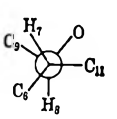
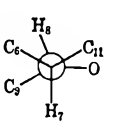
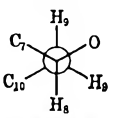
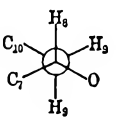
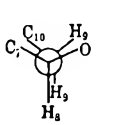
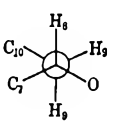
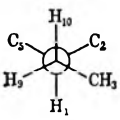
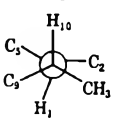
(47) M. T. Emerson, C. N. Caughlan, and W. Herz, *Tetrahedron Lett.*, 621 (1964); Mazhar-ul-Haque and C. N. Caughlan, *J. Chem. Soc. B*, 956 (1969).

(48) It should be noted that the internal shifts between "pseudoaxial" and "pseudoequatorial" protons on both bonds of floribundin have opposite signs when compared with corresponding internal shifts in the vermeerin spectrum.

(49) The symbol C_n refers to the atom lying in the plane of symmetry of the nondistorted boat or chair form of the cycloheptane ring.

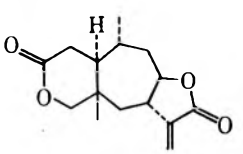
TABLE V

CONFORMATIONS OF VERMEERIN AND FLORIBUNDIN

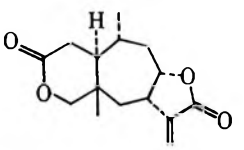
Fragment	C_1 boat[a] 1α, 5β, 7H-α, 8H-α	C_1 chair[b] 1α, 5β, 7H-β, 8H-β	C_5 chair[c] 1α, 5β, 7H-β, 8H-α	C_9 chair[d,e] 1α, 5β, 7H-α, 3H-β
C_2–C_1		*f*	*f*	*f*
C_4–C_5		*f*	*f*	*f*
C_6–C_7				
C_7–C_8				
C_8–C_9				
C_{10}–C_1		*f*		*f*

[a] Flexible, slightly folded. [b] Fixed by nonbonded interactions; seven-membered ring possesses normal, nondistorted conformation of "free" cycloheptane ring. [c] Flexible, interconvertible by twisting with C_6 chair which is excluded for steric reasons. [d] Fixed by transannular interaction of H_1 and H_2. [e] Twisted C_8 boat or C_6 flattened boat excluded by couplings H_6–H_7. [f] Conformation identical with that given in preceding column.

whereas in the C_1 boat of **3** there are the repulsions H-1 ⟷ H-7, H-8 and H-6 ⟷ H-10, H-9 (*endo*) to be considered.



2a

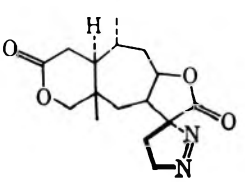


3a

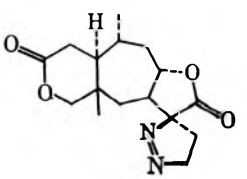
For vermeerin there are also only two possibilities with suitable conformations of the seven-membered ring, the C_5 chair form containing a pseudoequatorial C-10 methyl group and the relative stereochemistry of **2a**, and the C_9 chair form with the relative stereochemistry of **2**,[50] but in the C_5 chair form of **2a** the substituents on the C-8,C-9 bond are eclipsed which contradicts the observed splittings corresponding to $J_{8,9a}$ and $J_{8,9b}$ (Table III). Moreover, in this form the substituents on C-8,C-9 are staggered. This would result in strong puckering of the γ-lactone ring and affect the resonance stabilization adversely. Hence the C_9 chair of formula **2** is preferred. The decreased dihedral angles between H-1 and H-10 in this conformation explain the smaller value of $J_{1,10}$ in vermeerin.

The configurations of vermeerin and floribundin which have been deduced in the foregoing sections are supported by the CD curves of their pyrazolines. Inspection of the models shows that formation of a pyrazoline by reaction of floribundin (**3**) with diazomethane should occur predominantly, if not exclusively, from the α side to give **17**. On the basis of a recently deduced relationship[51] between the absolute configuration of such pyrazolines and the sign of their Cotton effect in the 330-nm region, one would expect a strongly positive CD curve for **17**. This was indeed observed ($[\theta]_{319}$ = 11,800).

The negative CD curve of the pyrazoline of vermeerin ($[\theta]_{324.5}$ = −10,000) indicates configuration **18**, formed by approach from the β side. Inspection of the model suggests that the β face of **2** (in the conformation deduced previously) is probably more accessible, but not so unambiguously so, as the α face of **3**.



17



18

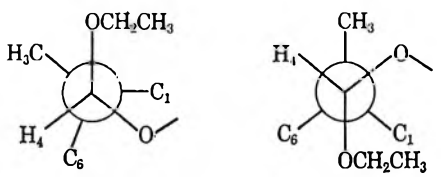
Hymenolide.—Comparison of the nmr spectrum (Tables II and III) of anhydrohymenolide (**10**) with the spectrum of floribundin suggested that the two compounds, and therefore hymenolide also, possessed the same stereochemistry at the common asymmetric cen-

(50) As noted previously, the magnitude of $J_{1,10}$ in vermeerin does not permit unequivocal determination of the configuration at C-10. However, leaving aside biogenetic arguments, comparison of Dreiding models of **2** and **2a** with models of their C-10 epimers indicates that the β configuration of the C-10 methyl group induces repulsions which makes this configuration inherently less probable.

(51) G. Snatzke, *Riechst., Aromen, Körperpflegem.*, **19**, 98 (1969); M. Suchy, L. Dolejs, V. Herout, V. Sorm, G. Snatzke, and J. Himmelreich, *Collect. Czech. Chem. Commun.*, **34**, 229 (1969).

ters C-1, C-5, C-7, C-8, and C-10. This was verified by the chemical correlation of **10** with themoidin (*vide supra*).

The probable configuration of **10** at C-4 could be deduced by taking into consideration the long-range couplings exhibited by the signal of H-4. Decoupling experiments revealed the absence of H-4,H-15 coupling, but it could be clearly demonstrated that $J_{3,4} \neq 0$. In order to account for this long-range coupling by the W path, H-4 should be pseudoequatorial as in U (six-membered ring, a half-boat) or in V (six-membered ring, a half-chair). Because of the presence of torsional strain in U, V (with H-4β) seemed more probable than U. This inference was also in accord with the indication that the δ-lactone ring of **9** is probably in the half-boat form (ir band of δ lactone superimposed on ir band of γ lactone at 1756 cm^{-1}), possibly because this allows the ethoxy group to occupy a pseudoequatorial position when the anomeric effect is minimized by introduction of the carbonyl group at C-3.



U V

The appearance of the H-3 signal of hymenolide as a doublet of doublets with $J_{2a,3} = 10.0$ and $J_{2b,3} = 2.5$ Hz (10.0 and 3.0 Hz in the case of **8b**) indicated that the C-3 hydroxyl group was equatorial and β. Hence, both oxygen functions on the hemiacetal ring of hymenolide are in the stable orientation, the C-3 hydroxyl group equatorial (β) and the C-4 ethoxy group axial and α (anomeric effect) as in **8a**. Furthermore, although the method of correlation of hymenoxynin with **8a** allowed for possible epimerization of hymenoxynin at C-4, the relative constancy in the chemical shift of H-4 and the presumed greater stability of an α-oriented acetal linkage at C-4 argue in favor of the proposition that the configuration of hymenoxynin at C-4 is the same as that of hymenolide, *i.e.*, as depicted in **14a**.

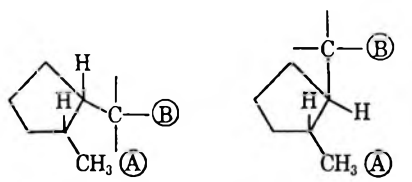
Greenein.—The infrared spectrum of greenein indicated that the δ-lactone ring (ir band at 1735 cm^{-1}) was in the half-chair form. Conformational analysis of the system in the manner described for vermeerin and floribundin was unfortunately not possible because the coupling constants $J_{1,2}$, $J_{1,10}$, and $J_{1,15}$ could not be determined and $J_{4,15}$, so important to establishing the nature of the ring junction in **2** and **3**, was necessarily absent. However, the close correspondence of the nmr spectra of greenein, **3** and **10** (see Tables II and III), indicated that the conformation of the seven-membered ring and the γ-lactone ring was probably the same.

Anthemoidin and Themoidin.—Anthemoidin (**4b**) and themoidin (**5a**) were identified as dihydro derivatives of vermeerin and floribundin, respectively. Two other dihydro derivatives were also encountered, 11-epianthemoidin (dihydrovermeerin A, **4a**) and 11-epithemoidin (**5b**).[52]

(52) **4a** was the only compound isolated when vermeerin was reduced with sodium amalgam–acetic acid. It was stable to base, as expected. Consequently, we were somewhat puzzled to find that themoidin, isolated in excellent yield by sodium amalgam reduction of floribundin, was isomerized by base treatment to a C-11 epimer **5b**. Obviously, in this instance, catalytic *and* sodium amalgam reduction afforded the less stable C-11 epimer.

The problem of solving the configuration of anthemoidin at C-11 relative to C-7 was solved by determining the magnitude of the coupling constant $J_{7,11}$.[42,53] The relative magnitudes of $J_{7,11}$ for **4a** (12.7 Hz) and **4b** (7.5 Hz) indicated that H-7 and H-11 are *cis* in anthemoidin (**4b**) and *trans* in its C-11 epimer (**4a**). The situation is not so simple in the case of themoidin and its C-11 epimer. We find $J_{7,11}$ for themoidin in the range of 8–9 Hz, an intermediate value (possibly due to greater flexibility of the *cis*-γ-lactone ring) which permits no clear decision regarding the steric relationship between H-7 and H-11. Moreover, the value of $J_{7,11}$ for 11-epithemoidin could not be determined accurately owing to overlapping of signals.

An alternative method for establishing the configuration at C-11 is based on the rule[54] that $^3J_{CH_3,H}$ for A,B *trans* < $^3J_{CH_3,H}$ for A,B *cis* (structure I), which apparently holds when the ring is five membered or smaller. The rule seems to be applicable to γ-lactones.[55] Comparison of the H-11, H-13 coupling constants of anthemoidin (6.6 Hz) and its C-11 epimer (7.5 Hz) leads to the same conclusion as before, *i.e.*, H-7 and H-11 *cis* for **4b** and *trans* for **4a**, but, while $J_{11,13}$ for themoidin was 7.3 Hz, the overlap, in the nmr spectrum of 11-epithemoidin, of the H-13 doublet and the H-6 multiplet interfered with the determination of $J_{11,13}$[56] and the application of the above method to determining the C-11 stereochemistry of themoidin.



H,H *cis* A,B eclipsed H,H *trans* A,B not eclipsed

Tentative assignment of formula **5a** to themoidin and **5b** to 11-epithemoidin is based on the relative chemical shift of H-11 in the two compounds. On the basis of a discussion of the conformation of saturated γ-lactones by Narayanan and Venkatasubramaniam[53] we suggest that H-11 is not affected significantly by the stereochemistry of the lactone ring *per se* and that its chemical shift should therefore be influenced primarily by the relative position of H-11 with respect to the shielding effects produced by the nearest anisotropic groups, *i.e.*, the bonds C-A,C-7 and C-7,C-B and the lactone group. However, it would be difficult to assess the separate contributions of these groups to the chemical shift of H-11 and to arrive at an *a priori* prediction of the sign of $\delta_{H\text{-}11\alpha} - \delta_{H\text{-}11\beta}$ which, granting the above argument, should remain constant.

While the literature does not contain many detailed analyses of nmr spectra of compounds with partial structure W, examination of the few examples which can be brought to bear on the problem (Table VI) sup-

(53) C. R. Narayanan and N. K. Venkatasubramaniam, *J. Org. Chem.*, **33**, 3156 (1968).

(54) J. Wolinsky, T. Gibson, D. Chan, and H. Wolf, *Tetrahedron*, **21**, 1247 (1965).

(55) Z. Samek, manuscript in preparation. Accurate measurement is necessary since the difference in $C_{11,13}$ coupling constants within a set of epimers is generally small.

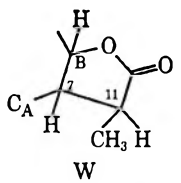
(56) In measuring INDOR spectra of H-13, signals of H-7 and H-11 change intensities since H-7 and H-11 overlap also and the estimation of $||^3J_{11,13} + {}^3J_{11,7}||$ becomes exceedingly difficult.

TABLE VI
CHEMICAL SHIFTS OF H-11

Compd	Stereochemistry	δ_{H-11}[a]
α-Santonin	H-6β, H-7α, H-11β	2.5[b]
β-Santonin	H-6β, H-7α, H-11α	2.76[b]
6-*epi*-α-Santonin	H-6α, H-7α, H-11β	2.55[b]
6-*epi*-β-Santonin	H-6α, H-7α, H-11α	2.92[b]
11-*epi*-Anthemoidin	H-7α, H-8β, H-11β	2.22[c]
Anthemoidin	H-7α, H-8β, H-11α	2.60[c]

[a] Ppm. [b] Reference 42. [c] This work.

ports the above assumption and leads to the tentative rule δ_{H-11} (H-7,H-11 *cis*) > δ_{H-11} (H-7,H-11 *trans*).[57] On this basis, themoidin (δ_{H-11} 2.92) is represented by formula **5a** and its C-11 epimer (δ_{H-11} 2.2) by **5b**.



W

Experimental Section[58]

Extraction of *Hymenoxys richardsonii* (Hook) Ckll. var. *floribunda* (Gray) Parker.—Above-ground material, wt 2.7 kg, collected by Dr. B. H. Braun in July 1962, in the vicinity of Boulder, Colo., was extracted with chloroform in the usual fashion.[59] The crude gum was chromatographed over 600 g of silicic acid, 800-ml fractions being collected. Fractions 1–15 (Bz, Bz–Chlf 3:1) eluted 2.4 g of oil, fractions 16–17 (Bz–Chlf 2:1) eluted 1.35 g of gum, and fractions 18–21 (Bz–Chlf 2:1) eluted 7.4 g of crystalline material. Recrystallization from Chlf–ether afforded vermeerin (**2**), mp 145–146°, $[\alpha]_D$ −67.1° (*c* 0.394), which had ir bands of 1766, 1729, and 1670 cm^{-1}, identical in all respects with authentic vermeerin. Vermeerin was not affected by treatment with hot acetic acid or boron trifluoride etherate.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.08; H, 7.57; O, 24.50.

Fractions 22–34 (Bz–Chlf 2:1 and 1:1) yielded 6.6 g of crystalline material. Recrystallization from acetone–ether afforded floribundin (**3**) which had mp 143°; $[\alpha]_D$ +84.0° (*c* 0.319); ir bands at 1757, 1727, and 1656 cm^{-1}; uv absorption λ_{max} 212.5 nm (ε 8300).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.19; H, 7.81; O, 24.69.

Fractions 76–82 (Bz–Chlf 1:3) afforded 0.85 g of yellow solid. Recrystallization from dioxane–ethyl acetate gave hispidulin (**1**) mp 290–293°, identical in all respects with authentic material from *Ambrosia hispida*. Further elution with Bz–Chlf or more polar solvents gave 25.1 g of gummy mixtures (tlc) which could not be separated satisfactorily.

The crude gum from 25 kg of *H. richardsonii* var. *floribunda*, collected by Mr. R. J. Barr on July 17, 1968, 10 miles southeast of Springerville, Apache County, Ariz., at 7500-ft elevation (Barr No. 68363, on deposit in herbarium of Florida State University) weighed 685 g. A 280-g portion was chromatographed over 2.6 kg of silicic acid in the usual way. Fractions 1–8 (Bz, Bz–Chlf 1:2) gave 7.0 g of gum and fractions 9–38 (Bz–Chlf 1:2 to Chlf) gave 23.6 g of crude vermeerin. Fractions 39–60 (Chlf to Chlf–MeOH 93:7) gave 121 g of a gum which contained several compounds including apparently some floribundin (tlc). Successive elution with Chlf–MeOH (93:7, fractions 61–62) gave 90 g of gummy mixture. Efforts to separate the constituents of these fractions are under way. Fractions 63–67 (Chlf–MeOH 93:7) gave a yellow solid which on recrystallization afforded 2.47 g of hispidulin. Further elution with methanol gave a gummy mixture.

Pyrazoline of Vermeerin—Vermeerin, wt 136 mg, in 40 ml of anhydrous ether and 1 ml of methanol was mixed with excess diazomethane in ether and left in the refrigerator for 4 days. Evaporation at reduced pressure afforded 142 mg of solid which was recrystallized from ethyl acetate. The product had mp 125–126° dec, ir bands at 1776 and 1730 cm^{-1}, CD curve (c 0.7 mg/30 ml), $[\theta]_{324.5}$ −10,000.

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24. Found: C, 62.73; H, 7.34.

Pyrazoline of Floribundin.—Treatment of 220 mg of floribundin with diazomethane in the manner described in the previous paragraph gave 243 mg of crude pyrazoline. Recrystallization from ethyl acetate–chloroform yielded colorless needles which had mp 134–135° dec, ir bands at 1775 and 1735 cm^{-1}, CD curve (c 1.18 mg/25 ml), $[\theta]_{319}$ +11,800.

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 63.27; H, 7.07; N, 8.80.

Reduction of Vermeerin. (A).—A solution of 601 mg of vermeerin in 10 ml of acetic acid was reduced in a hydrogen atmosphere with 71 mg of platinum oxide for 1.5 hr, and was filtered and evaporated. The residue was taken up in dichloromethane, washed and evaporated, and the crude product, wt 0.6 g, chromatographed over 120 g of silica gel, 80-ml fractions being collected. Fractions 1–10 (Bz–ether 17:3) eluted nothing, fractions 11–89 (same eluent) afforded 382 mg of solid dihydrovermeerin A (**4a**) which was recrystallized from acetone–ether and then had mp 128°, $[\alpha]_D$ −25.7° (*c* 0.247); ir bands at 1774 and 1732 cm^{-1}; mol wt 266 (mass spectrometry). It was recovered unchanged after heating for 1 hr with sodium methoxide in methanol and subsequent acidification.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33; O, 24.03. Found: C, 67.79; H, 8.38; O, 23.67.

Continued elution with Bz–ether (17:3) gave, in fractions 90–137, 45 mg of a solid mixture of dihydrovermeerin A and B and a third substance C, and, in fractions 138–220, 150 mg of a mixture of dihydrovermeerin B and the third substance C, which was rechromatographed over 40 g of silica gel (40-ml fractions eluent Bz–ether 4:1). Fractions 121–145 eluted 86 mg of dihydrovermeerin B (**4b**) which was recrystallized from acetone–ether and had mp 213–214°. Direct comparison established identity with anthemoidin from *Hymenoxys anthemoides*. Fractions 180–235 eluted 62 mg of the third substance which was recrystallized from acetone–ether and had mp 177–179°, ir bands at 1767 and 1735 cm^{-1}, mol wt 266 (mass spectrometry). Because of the small quantity available, the nmr spectrum could not be determined. We are unable to account for the formation of a third substance but the small amount available prevented further investigation of the apparent discrepancy.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.78; H, 8.27.

(B).—To a solution of 100 mg of vermeerin in 7 ml of ethanol and 0.1 ml of acetic acid was added in small portions 2.5 g of 3% sodium amalgam. After 3 hr, the mixture was separated from mercury, filtered, and evaporated *in vacuo*. The residue was taken up in chloroform, washed, dried, and evaporated. The residue, wt 0.1 g, melted at 123–124° after recrystallization from acetone–ether and was identical with dihydrovermeerin A in all respects.

Reduction of Floribundin. (A).—A solution of 2.0 g of floribundin in 130 ml of ethanol and 1 ml of acetic acid was stirred with 57 g of 3% sodium amalgam for 3 hr and worked up as described in the preceding paragraph. The crude product, wt 2.0 g (two major spots on tlc), was recrystallized from acetone–ether to give 1.15 g of a dihydroderivative [dihydrofloribundin A (**5**)] which had mp 213° and was identical in all respects with themoidin isolated from *H. anthemoides*. The mother liquors contained

(57) Z. Samek and W. Herz, unpublished work. The validity of this rule is presently under investigation; the results will be the subject of a futnre communication.

(58) Melting points are uncorrected. Rotations were run in methanol unless otherwise specified, ultraviolet spectra in 95% ethanol on a Cary Model recording spectrophotometer, infrared spectra in chloroform unless otherwise specified on a Perkin-Elmer Model 257 grating spectrometer, CD curves in methanol on a Jasco ORD/UV-5 recording spectrometer, mass spectra on a Nuclide 12-in. medium resolution mass spectrometer, and routine nmr spectra on a Varian A-60 spectrometer in deuteriochloroform solution with tetramethylsilane serving as internal standard. Analyses were performed in the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences or by Dr. F. Pascher, Bonn, Germany. Silicic acid was Mallinckrodt 100 mesh; petroleum ether was low boiling (30–60°). Chromatographic fractions were routinely monitored and products were checked for purity by tlc on microslides coated with silica gel G. Spots were detected by spraying with concentrated sulfuric acid followed by heating. The following abbreviations are used for chromatographic separations: Bz, benzene; Chlf, chloroform; MeOH, methanol.

(59) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

a mixture of themoidin and other products which could not be separated satisfactorily by chromatography.

(B).—Catalytic hydrogenation of 70 mg of floribundin in 40 ml of acetic acid with 100 mg of platinum oxide at 30 lb/in.^{2} and work-up in the usual way gave a single spot on tlc. Recrystallization from acetone–ether yielded 53 mg of themoidin, mp 212–214°. Similarly, hydrogenation of 55 mg of floribundin (ethanol, palladium on charcoal) gave a gum (single spot on tlc) which was chromatographed over 12 g of silicic acid. Elution with benzene–wet ether (19:1) afforded a solid (single spot on tlc) which after recrystallization gave 43 mg of themoidin, mp 214–215°.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33; O, 24.03. Found: C, 67.56; H, 8.30; O, 24.62.

11-Epithemoidin (5b).—A solution of 0.5 g of themoidin in 5 ml of methanol containing 0.05 g of sodium was heated for 1 hr, cooled, diluted with water, acidified with dilute sulfuric acid, and extracted with chloroform. The washed and dried organic layer was evaporated and the residual solid (1:3 mixture of **5a** and **5b**) was purified by preparative tlc (silica gel–ether). Recrystallization from acetone–ether afforded 0.28 g of 11-epithemoidin which had mp 146–147°; $[\alpha]_D$ +54.1° ($CHCl_3$, *c* 1.02); ir bands at 1762 and 1732 cm^{-1}; nmr signals at 4.36 m (H-8), 3.92 (AB system, line separation 11.5 Hz, H-4a and H-4b), 1.31 d (J = 7.5 Hz), and 1.08 d (J = 7.5 Hz, C-10 and C-11 methyl), and 1.08 ppm (C-5 methyl).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33; O, 24.03. Found: C, 68.32; H, 8.02; O, 23.94.

Extraction of *Hymenoxys anthemoides* (Juss.) Cass.—Above-ground material, wt 3.6 kg, collected by Mr. P. R. Legnamé and Mr. A. R. Cuezzo on Dec 23, 1965, 4 miles from Santa Rosa at the junction of the road to Bella Vista and on Oct 24, 1966, at kilometer 42 along the road from Santa Rosa to Leales, Department of Leales, Tucuman Province, Argentina (Legnamé and Cuezzo No. 5502 and 5595 on deposit in herbarium of Instituto Miguel Lillo, Tucuman, Argentina), was extracted in the usual manner. The crude gum, wt 64 g, was taken up in 100 ml of benzene and chromatographed over 800 g of silicic acid, 800-ml fractions being collected. Fractions 1–35 (Bz or Bz–Chlf 3:1) eluted nothing and 4.6 g of oil. Fractions 36–45 (Bz–Chlf 3:1) eluted 7.5 g of solid material which after recrystallization from acetone–ether melted at 145–146° and was identified as vermeerin. Fractions 46–58 (Bz–Chlf 3:1) gave 5.1 g of solid which after recrystallization melted at 143° and was identified as floribundin. Fractions 59–70 (Bz–Chlf 3:1) eluted 2.95 g of a mixture of anthemoidin and themoidin (*vide infra*). Fractions 71–142 (Bz–Chlf 2:1, 1:1, 1:2, and 1:3) gave 4.8 g of gum. Fractions 143–169 (Chlf) eluted a trace of gum. Fractions 170–234 (Chlf–MeOH 99:1 to MeOH) eluted 7.35 g of gum.

Rechromatography of the material from fractions 59–70 over 100 g of silicic acid (5-ml fractions of benzene containing increasing proportions of ether) gave in fractions 43–75 (Bz–ether 5:1) 50 mg of anthemoidin which had mp 220–221° after recrystallization from chloroform–ether; $[\alpha]_D$ −115.5° (*c* 0.139); ir bands at 1780 and 1735 cm^{-1}; mol wt 266 (mass spectrometry). It was subsequently shown to be identical with dihydrovermeerin B.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.68; H, 8.38.

Fractions 76–82 (5:1) eluted nothing, fractions 83–139 (5:1) eluted 170 mg of mixture, fractions 140–159 (5:1) eluted 25 mg of themoidin which had mp 219–220° (decreasing to 213–214° on storage) after recrystallization from acetone–ether; $[\alpha]_D$ +61.8° ($CHCl_3$, *c* 0.55); mol wt 266; ir bands 1767 and 1731 cm^{-1}. This substance was subsequently shown to be identical with dihydrofloribundin.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33; O, 24.03. Found: C, 67.61; H, 8.27; O, 23.76.

Extraction of *Hymenoxys greenei* (Ckll.) Rydb.—Above-ground plant, wt 3.1 kg, collected by Dr. H. F. L. Rock on July 5, 1960, on Arizona State Route 65, 42 miles south of Winslow (Rock No. 1104, on deposit in herbarium of Vanderbilt University) was extracted in the usual manner, yield of crude gum 65 g. A 45-g portion was chromatographed over 450 g of aluminum (500-ml fractions), but none of the eluates gave solid. The gummy material eluted with Bz, Bz–Chlf, and Chlf (wt 22 g) was rechromatographed over 450 g of silicic acid (1000-ml fractions). None of the fractions crystallized, and only the material from fractions 53–56 (Bz–Chlf 1:3) and 63–74 (Bz–Chlf 1:3) and 75–82 (Bz–Chlf 1:3) appeared to be reasonably homogeneous (tlc).

Rechromatography of the gum from fractions 53–56 over 60 g of silicic acid gave, in the fraction eluted with benzene–wet ether (19:1), a solid which was recrystallized from acetone–ether to give 220 mg of greenein (**6**): mp 169–171°; ir bands at 1770, 1735, and 1660 cm^{-1}. Rechromatography over silicic acid and elution with Bz–Chlf (3:1) raised the melting point to 175–176°, $[\alpha]_D$ +114° (*c* 0.2845).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.09; H, 7.59.

Rechromatography of the gum from fractions 63–74 over 170 g of silicic acid gave in the fraction eluted with benzene–wet ether (7:3), a solid which was recrystallized from acetone–ether to give 180 mg of floribundin, mp 142–144°, identical in all respects with the material isolated from *H. richardsonii* var. *floribunda*. Rechromatography of the gum from fraction 75–82 over 60 g of silicic acid gave, in the fraction eluted with benzene–wet ether (100:3), a gum which partially solidified on trituration with ether–hexane (1:1). Recrystallization from acetone–ether afforded 15 mg of an unknown solid, mp 244–246° after recrystallization from acetone–ether.

Hydrogenation of Greenein.—A solution of 40 mg of greenein in 25 ml of ethanol was hydrogenated at 30 lb/in.^{2} with 50 mg of palladium on charcoal. The usual work-up gave a gum which was chromatographed over 10 g of silicic acid. Elution with benzene–wet ether (19:1) gave a solid which was recrystallized from acetone–ether–hexane and had mp 103–105°; ir bands at 1770 and 1735 cm^{-1}; nmr signals a 4.7 m (H-8), 4.35 m (2 protons, H-3), 1.30 (C-5 methyl), and 1.15 d (C-10 and C-11 methyls).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 68.06; H, 8.55.

Extraction of *Hymenoxys odorata* DC. (A).—Above-ground material, wt 3.6 kg, collected by Mr. J. L. Strother in July 1965 on Route 54, 17 miles south of Saltillo, Coahuila, Mexico (Strother No. 451 on deposit in herbarium of University of Texas at Austin), was extracted with chloroform in the usual manner. The crude gum, wt 69 g, was taken up in 100 ml of benzene and chromatographed over 900 g of silicic acid (800-ml fractions). Fractions 1–26 (Bz to Bz–Chlf 3:1) eluted nothing. Fractions 27–247 (Bz–Chlf 3:1 to Chlf–MeOH 97:3) gave 47.5 g of gum. Fractions 246–250 (Chlf–MeOH 97:3) eluted 1.85 g of solid material. Recrystallization from acetone afforded 1.2 g of hymenoxynin as colorless needles: mp 125–128°; $[\alpha]_D$ −37.6° (pyridine, *c* 0.93); ir bands at 3420 (very strong) and 1770 cm^{-1}; nmr signals (100 MHz, $CDCl_3$–DMSO-d_6 + DOAC) 4.70 m (H-8), 4.47 d (J = 7.5 Hz, α-anomeric H of glucose), 4.35 (H-4), 3.2–4.05 m (8 H, H-2, H-2′, H-3′, H-4′, H-5′, and H-6′ of glucose residue), 1.11 d (J = 6.5 Hz), and 1.05 d (J = 6 Hz, C-10 and C-11 methyls), 0.99 ppm (C-5 methyl).

Anal. Calcd for $C_{21}H_{34}O_9 \cdot H_2O$: C, 56.24; H, 8.09; O, 35.67. Found: C, 56.21; H, 8.06; O, 35.99.

(B).—Above-ground material, wt 22.5 kg, collected by Mr. R. J. Barr on June 16–23, 1968, 1 mile east of Rodeo, Hidalgo County, N. M. (Barr No. 68307 on deposit in herbarium of Florida State University), was extracted in the usual manner. The yield of crude gum was 450 g. A 250-g portion was taken up in benzene and chromatographed over 2.5 kg of silicic acid (800-ml fractions). Fractions 1–29 (Bz and Bz–Chlf) eluted 15.6 g of oily material. Fractions 30–85 (Bz–Chlf 2:1 and 1:1) gave 65 g of gum containing hymenolide (*vide infra*). Further elution with Bz–Chlf 1:1 to Chlf–MeOH 97:3 (fractions 86–142) gave 120 g of gum. Fractions 143–150 (Chlf–MeOH 97:3) gave a yellow solid which was recrystallized from dioxane–ethyl acetate to give yellow needles, mp 290–293° dec, wt 0.298, which were identified as hispidulin by comparison with authentic material and conversion to hispidulin triacetate, mp 168–170°. Fractions 151–163 (Chlf–MeOH 9:1) gave 58 g of gum. Further elution with the same solvent (fractions 164–166) gave solid material, wt 3.2 g, which was recrystallized from methanol and then melted at 177–179°: $[\alpha]_D$ +64.4° (pyridine, *c* 0.9); ir bands at 3600–3200 (hydroxyl), 1750, 1660 (conjugated γ-lactone), 1738 (cyclopentanone), and 1720 cm^{-1} (acetate); nmr signals (100 MHz, $CDCl_3$–DMSO-d_6) 6.16 d (J = 2.5 Hz) and 5.14 d (J = 2.0 Hz, exocyclic methylene), 4.95 d (4.0), 4.81 d (J = 3.8 Hz), and 4.64 d (J = 4.0 Hz, hydroxyl protons in glucose residue, disappeared on exchange with deuterioacetic acid), 4.37 (J = 7.0 Hz, H-1), 3.50 (2 protons, CH_2OAc), 2.03 (acetate), 1.34 d (J = 6 Hz, C-10 methyl), and 0.94 ppm (C-5 methyl). This substance was identified as paucin by direct comparison with an authentic sample and by its reactions (*vide infra*). Further elu-

tion (Chlf–MeOH 9:1 to MeOH) provided 6.8 g of gummy material.

Rechromatography of the gum from fractions 30–85 over 800 g of silica gel (800-ml fractions) provided in fractions 1–30 (Bz to Bz–Chlf 10:3) 13.8 g of gummy mixture; continued elution (Bz–Chlf 10:3 to Bz–Chlf 1:1, fractions 31–77) gave solid. Recrystallization from ethyl acetate furnished 7.3 g of hymenolide (**8a**) which had mp 136–138°; $[\alpha]_D$ −48.6° ($CHCl_3$, *c* 1.4); ir bands at 3570, 3445, 1750, and 1660 cm^{-1}; nmr signals at 6.31 d (J = 2.5 Hz) and 5.60 (J = 2.0 Hz, exocyclic methylene conjugated with lactone), 5.11 d br, sharpens to dd (J_1 = 10.0, J_2 = 2.5 Hz) on addition of D_2O (H-3), 4.38 d (7.5, disappears on exchange, −OH), 4.31 (H-4), 4.1–3.3 c (nonequivalent CH_3CH_2O, confirmed by spin decoupling at 90 MHz), 1.25 t (J = 7.0 Hz, CH_3–CH_2O), 1.09 d (J = 7.0 Hz, C-10 methyl), and 1.05 ppm (C-5 methyl).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44; O, 25.78. Found: C, 65.77; H, 8.61; O, 25.84.

Further elution gave 38.4 g of gummy mixture.

Anhydrohymenolide (10).—Acetylation of 126 mg of hymenolide with pyridine–acetic anhydride afforded a gum (**8b**) which could not be induced to crystallize: ir bands at 1760 (double strength, lactone and acetate) and 1220 cm^{-1}; nmr signals at 6.26 d (J = 2.5 Hz) and 5.57 d (J = 2 Hz, exocyclic methylene), 6.08 dd (J_1 = 10, J_2 = 2 Hz, H-3), 4.77 m (H-8), 4.31 (H-4), 3.3–4.2 c (2 protons, $-OCH_2CH_3$), 2.10 (acetate), 1.28 t (J = 7.0 Hz, $-OCH_2CH_3$), 1.10 d (J = 5.3 Hz, C-10 methyl), and 1.07 ppm (C-5 methyl).

The above substance, wt 810 mg, was heated at 190–200° in a nitrogen atmosphere for 1.5 hr. The solid product **10**, yield 695 mg, was recrystallized from petroleum ether–ether and then melted at 82–83°: $[\alpha]_D$ −146.4° ($CHCl_3$, *c* 1.195); ir bands at 1762 (γ-lactone) and 1662 cm^{-1} (strong, two double bonds).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27; O, 21.89. Found: C, 69.83; H, 8.23; O, 22.07.

Hydrogenation of Anhydrohymenolide.—A solution of 110 mg of **10** was hydrogenated with 60 mg of PtO_2 at room temperature for 6 hr. Filtration followed by evaporation *in vacuo* gave a gum which was chromatographed over 12 g of silica gel (40-ml fractions). Fractions 1–14 (petroleum ether–Bz 1:1 and Bz) yielded a trace of gum. Fractions 15–25 (Bz–Chlf 5:1 to 2:1) gave 50 mg of solid material (single spot on tlc) which after recrystallization from petroleum ether melted at 73–75° and was identical in all respects with **15b** from hydrolysis of hymenoxynin with ethanolic HCl. Further elution with Bz–Chlf 2:1 and 1:1 gave 42 mg of solid **16** (single spot on tlc) which was recrystallized from ethyl acetate–petroleum ether and had mp 154.5–156°; $[\alpha]_D$ −121.2° ($CHCl_3$, *c* 0.85); ir bands at 1738 and 1661 cm^{-1}; nmr signals at 5.00 m (H-8), 4.28 (H-4), 3.67 c (4 protons, H-3 and CH_3CH_2O–), 1.85 br (C-11 methyl), 1.24 t (J = 7 Hz, CH_3CH_2O–), 0.93 (C-5 methyl), and 0.90 d (J = 6 Hz, C-10 methyl).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90; O, 21.74. Found: C, 69.30; H, 8.72; O, 21.63.

Dehydrochymenolide (9).—A solution of 263 mg of hymenolide in 1.5 ml of pyridine was added to 245 mg of CrO_3 in 1 ml of pyridine, set aside at room temperature overnight, diluted with water, and extracted with ethyl acetate. The organic layer after washing and drying furnished 234 mg of solid material which was recrystallized from ethyl acetate and had mp 178–181°; $[\alpha]_D$ −56.2° (*c* 0.925, $CHCl_3$); ir bands at 1756 and 1661 cm^{-1}; nmr signals at 6.32 d (J = 2.5 Hz) and 5.60 d (J = 2.0 Hz, exocyclic methylene group), 4.78 m (H-8), 4.78 (H-4), 3.4–4.2 m (2 protons, CH_3CH_2O–), 1.28 t (J = 7 Hz, CH_3CH_2O–), 1.10 d (J = 6 Hz, C-10 methyl), and 1.05 ppm (C-5 methyl).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84; O, 25.94. Found: C, 66.40; H, 7.88; O, 25.82.

Oxidation of 305 mg of hymenolide in 2 ml of acetone with 6 ml of Jones reagent at room temperature and work-up in the usual fashion gave, in the neutral fraction, 97 mg of **9**, mp 178–181°. The acid fraction afforded 83 mg of deethyldehydrohymenolide (**11**), mp 145–146° (*vide infra*).

Deethyldehydrohymenolide (11).—A solution of 87 mg of **8a** in 1.5 ml of acetone–water (4:1) and 0.5 ml of concentrated HCl was allowed to stand at room temperature for 5 hr, diluted with water, and extracted with ethyl acetate. Evaporation of the washed and dried extract afforded 80 mg of **11** which was recrystallized from ethyl acetate and melted at 145–146°: $[\alpha]_D$ −2.7° (*c* 0.74, $CHCl_3$); ir bands at 1753a and 1660 cm^{-1}; nmr signals at 6.33 d (J = 2.5 Hz) and 5.68 d (J = 2 Hz, exocyclic methylene), 5.23 (H-4), 4.81 m (H-8), 1.09 d (J = 7 Hz, C-10 methyl), and 1.03 ppm (C-5 methyl).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; O, 28.54. Found: C, 63.93; H, 7.16; O, 28.84.

$NaBH_4$ Reduction of 11.—A solution of 370 mg of **11** in 3 ml of methanol was allowed to stand overnight with an excess of $NaBH_4$, diluted with water, acidified with dilute HCl solution, and extracted with ethyl acetate. The washed and dried extract was evaporated at reduced pressure and the residue recrystallized from acetone. The first crop consisted of 86 mg of themoidin (dihydrofloribundin, **5a**), mp 212–214°, which was identical in all respects with an authentic sample. The material in the mother liquors was recrystallized from ethyl acetate. This afforded 63 mg of floribundin, mp 142–143°, which was identical in all respects with an authentic sample.

Reactions of Paucin. (A).—A solution of 70 mg of paucin in 1 ml of absolute pyridine and 0.5 ml of acetic anhydride was allowed to stand at room temperature overnight, diluted with water, and extracted with ethyl acetate. The washed and dried extracts were evaporated and the residual solid, wt 98 mg, was recrystallized from methanol. Triacetylpaucin had mp 240–242° (lit. 241–243°); $[\alpha]_D$ +38.8° (pyridine, *c* 0.8); ir bands at 1755 (very strong); 1224 nmr signals at 6.37 (J = 2.5 Hz) and 5.78 (J = 2 Hz, exocyclic methylene), 5.5–3.8 c (9 protons), 2.12, 2.07, 2.03 (acetates), 1.20 d (J = 6.0 Hz, C-10 methyl), and 0.98 ppm (C-5 methyl).

(B).—A mixture of 0.3 g of paucin, 5 ml of acetic acid, and 5 ml of water was refluxed for 5 hr until all starting material had disappeared (tlc); the mixture was cooled, diluted with water, and extracted with ethyl acetate. The washed and dried extract was evaporated and the gummy residue, wt 223 mg, was chromatographed over 10 g of silica gel. Benzene (2 fractions, 40 ml each) eluted a trace of gum; fractions 3–5 (benzene–ethyl acetate, 10:1) eluted 110 mg of solid which was recrystallized from ethyl acetate, mp 160–162° (lit. mp 159–160°). Mixture melting point and ir and nmr spectrum identified this substance as aromatin (**12**).[27]

Tetraacetylhymenoxynin (14b).—Acetylation of 68 mg of hymenoxin with 1 ml of absolute pyridine and 0.5 ml of acetic anhydride at room temperature overnight followed by dilution with water and extraction with ethyl acetate yielded, after washing and drying of the organic extract and evaporation *in vacuo*, 113 mg of solid tetraacetate. The product was recrystallized from ethyl acetate and had mp 176–177°; $[\alpha]_D$ +15.6° ($CHCl_3$, *c* 0.96); nmr signals (100 MHz, $CDCl_3$), 5.13 c (3 superimposed protons, –CHOAc), 4.79 d (J = 7 Hz, H_2, α-anomeric proton) superimposed on 4.7 c (2 protons, H-8 and –CHOAc), 4.20 (H-4) superimposed on 4.3–4.0 c (2 protons), 3.95 and 3.86 m (2 protons, H-3), 2.08, 2.03, 2.03, 2.00 (4 acetates), 1.14 d (J = 7 Hz), and 1.07 d (J = 7 Hz, C-10 and C-11 methyls), 1.00 ppm (C-5 methyl).

Hydrolysis of Hymenoxynin. (A).—A mixture of 200 mg of hymenoxynin, 2 ml of methanol, and 1 ml of concentrated HCl was allowed to stand at room temperature overnight, diluted with water, and extracted with ethyl acetate. Evaporation of the washed and dried extract furnished 110 mg of **15a** which was recrystallized from ether–petroleum ether and had mp 113–114°; $[\alpha]_D$ −83.5° ($CHCl_3$, *c* 0.635); ir bands 2828 (methoxyl), 3.70 and 2.93 m (H-3), 1.14 d (J = 6 Hz) and 1.10 (J = 5.5 Hz, C-10 and C-11 methyl), 1.07 ppm (C-5 methyl).

Anal. Calcd for $C_{16}H_{28}O_4$: C, 68.55; H, 8.63; O, 22.83. Found: C, 68.43; H, 8.95; O, 23.17.

The aqueous layer from the hydrolysis was concentrated to 20 ml at reduced pressure, neutralized with 0.2 g of $CaCO_3$, filtered, and evaporated at reduced pressure. The residue, wt 0.18 g, was mixed with 0.2 g of phenylhydrazine hydrochloride, 0.3 g of sodium acetate, and 2 ml of water, heated on the water bath for 10 min, cooled, and filtered. The yellow product was recrystallized from methanol and identified as glucosazone, mp 210–211°, by comparison with an authentic sample prepared from D-(+)-glucose in the usual manner.

Hydrolysis of 115 mg of the acetal **15a** with 1 ml of acetone–water (4:1) and 0.5 ml of concentrated HCl at room temperature for 2 days, dilution with water, extraction with ethyl acetate, and processing of the organic extract in the usual way resulted in 120 mg of a crude lactol **15c**. Recrystallization from acetone furnished 86 mg of which had mp 318–320° dec; $[\alpha]_D$ −118.4° ($CHCl_3$, *c* 0.38); ir bands at 3490, and 1762 cm^{-1}; nmr signals at 4.85 m (H-8), 4.51 (H-4), 3.75 and 2.95 m (H-3), 1.16 (C-5 methyl), 1.14 d and 1.11 d (J = 6.0 Hz, C-10 and C-11 methyls).

(B).—Hydrolysis of 128 mg of hymenoxynin in the manner described in the previous section using ethanolic HCl and work-up in the usual fashion furnished, after recrystallization from petroleum ether, the ethoxy derivative **15b** which had mp 73–75°; $[\alpha]D$ −94.1° ($CHCl_3$, *c* 0.85); nmr signals at 4.77 m (H-8), 4.12 (H-4), 3.35–4 c (3 protons, H-3a and CH_3CH_2O–), 3.0 m (H-3b), 1.22 t (J = 7 Hz, CH_3CH_2O–), 1.15 (J = 5 Hz,) and 1.08 d (J = 5.5 Hz, C-10 and C-11 methyl), and 1.06 ppm (C-5 methyl).

This substance was identical in all respects with the less polar material obtained by hydrogenation of anhydrohymenolide (10).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.69; H, 9.52; O, 21.59. Found: C, 68.80; H, 9.45; O, 21.66.

Registry No.—**2**, 16983-23-6; **3**, 25062-22-0; **4a**, 25062-24-2; **4b**, 25062-25-3; **5a**, 25062-26-4; **5b**, 25062-27-5; **6**, 25080-56-2; **7**, 25062-28-6; **8a**, 25062-29-7; **8b**, 25062-30-0; **9**, 25062-31-1; **10**, 25062-32-2; **11**, 25062-33-3; **14a**, 25062-34-4; **14b**, 25062-35-5; **15a**, 25062-36-6; **15b**, 25062-37-7; **15c**, 25062-38-8; **16**, 25080-57-3; **17**, 25062-23-1; **18**, 25062-40-2.

Conversion of Solasodine to Solafloridine and Dihydrosolacongestidine Acetate

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The two major steroidal alkaloids, solafloridine and solacongestidine, isolable from *Solanum congestiflorum* have been synthesized from solasodine. In the conversion acetylsolasodine is reduced to 3-acetyltetrahydrosolasodine, converted to the N-carbobenzoxy derivative, and oxidized to the 3-acetyl-16-oxo-N-carbobenzoxy compound. Sodium–propanol reduction affords the desired 16α epimer, dihydrosolafloridine, convertible to solafloridine by dehydrohalogenation of the N-chloro derivative. Thioketalization of the 3-acetyl-16-oxo-N-carbobenzoxy compound followed by Raney nickel reduction yields dihydrosolacongestidine acetate.

In a recent publication,[2] the isolation and structure proof of the steroidal alkaloids, solacongestidine (I) and solafloridine (II), from *Solanum congestiflorum* were reported. Owing to the time-consuming, laborious procedure involved in isolation and poor yield of the alkaloids from the plant, an alternate source was sought for these compounds when a demand for more alkamine, particularly solafloridine (II), arose for other projects.

Starting from solasodine[3] (III), a readily available steroidal alkaloid having the correct stereochemical configuration, the conversion was achieved in the following manner. O-acetylsolasodine[4] (IV) prepared from the reaction of solasodine (III) with acetic acid containing *p*-toluenesulfonic acid was reduced with sodium borohydride to O-acetyldihydrosolasodine (V) and in turn reduced catalytically (Pd–C) to O-acetyltetrahydrosolasodine[5] (VI). Conversion of VI to the N-carbobenzoxy-3-acetyl derivative (VII) with carbobenzoxy chloride and oxidation with Kiliani's reagent[6] in acetone to the 16-oxo compound (VIII) followed by reduction with sodium–2-propanol afforded the 16α-hydroxyl bearing dihydrosolafloridine[2] (IX) in good yields. A somewhat lesser yield was obtained by reduction with lithium–ammonia. This was accounted for by the recovery of considerable deacetylated starting material, VIIIa.[7] Compound IX, thus prepared, agreed in properties (melting point, mixture melting point, ir) with that obtained from the reduction of the natural product. The pathway outlined above, we believe, is an improvement over the published partial synthetic procedure[8] since the stereochemistry at C-20 and C-25 is unaffected throughout these reactions. The yield of the N-carbobenzoxy compound (VII) is diminished somewhat by the formation of a by-product assigned the structure XII either formed by the interaction of VI with some phosgene liberated during the reaction or ring closure of the debenzyloxy product of VII with the C_{16}–OH function.[9] The structure of XII was confirmed by its synthesis from the reaction of VI with phosgene. It should be noted in passing that the sodium borohydride reduction of the 16-oxo compound VIII afforded only the 16β-hydroxy isomer, VII, as expected.

Finally dihydrosolafloridine (IX) was converted to solafloridine (II) by dehydrohalogenation of the N-chloro compound in the manner reported by Schreiber and Adam.[8]

The N-carbobenzoxy-16-oxo compound (VIII) served as a convenient starting point for the preparation of dihydrosolacongestidine acetate (XI). This was accomplished by thioketalization of VIII with ethanedithiol which yielded the crystalline thioketal X. Desulfurization of the thioketal moiety with Raney nickel led to concomitant elimination of the N-carbobenzoxy function to afford the desired dihydrosolacongestidine acetate[2] (XI). Compound XI exhibited properties (melting point, mixture melting point, ir, mass spectrum) indistinguishable from those derived from solacongestidine. The compound like dihydrosolafloridine

(1) Visiting Scientists: G. Kusano (1969–present) and N. Aimi (1968–1969).

(2) Y. Sato, H. Kaneko, E. Bianchi, and H. Kataoka, *J. Org. Chem.*, **34**, 1577 (1969).

(3) For a general review, see K. Schreiber in "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, Chapter 1.

(4) We are indebted to Dr. J. A. Beisler of this laboratory for working out this procedure. H. Rochelmeyer, *Arch. Pharm.* (Weinheim), **277**, 329 (1939), report mp 193–194°.

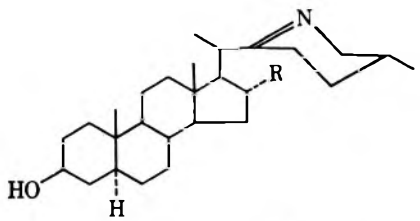
(5) Compound VI can also be prepared in somewhat reduced yields by the direct catalytic reduction (PtO_2–HAc) of O-acetylsolasodine (IV).

(6) H. Kiliani, *Ber.*, **46**, 676 (1913). A solution of 53 g of chromium trioxide and 80 g of concentrated sulfuric acid in 400 g of water was used.

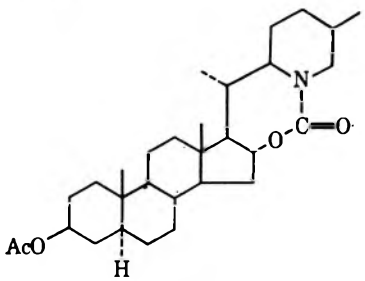
(7) In two runs the yield of the deacetylated starting material, VIIIa, was approximately the same. Perhaps the insolubility of the compound prevents its further participation in the reaction. We intend to study this reaction further.

(8) K. Schreiber and G. Adam, *Justus Liebigs Ann. Chem.*, **666**, 176 (1963).

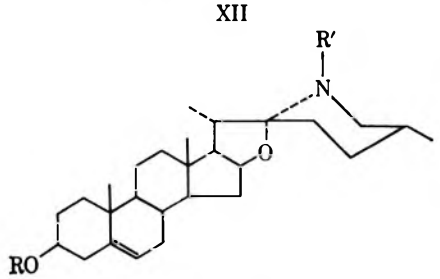
(9) It was suggested by one of the referees that formation of XII could have resulted from the attack of 16β-OH on the carbonyl function of the carbobenzoxy group of VII followed by loss of the benzyloxy ion. However, we had observed that in the repeat runs, vigorous agitation or stirring of the reaction flask resulted in negligible yields of XII. Hence, it was thought that in the earlier runs, due to insufficient agitation of the immiscible phase, neutralization was incomplete, and the resulting local acidic conditions led to prior debenzyloxylation.



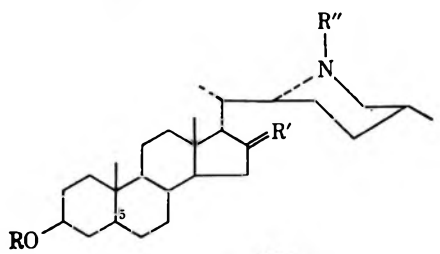
I (solacongestidine), R = H
II (solafloridine), R = OH

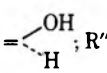


XII

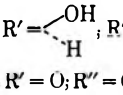


III, (solasodine), R = R′ = H
IV, R = Ac, R′ = H



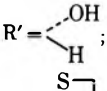
V (Δ^5), R = Ac; R′ =  ; R″ = H

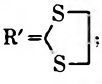
VI ($C_5\alpha$), R = Ac; R′ =  ; R″ = H

VII ($C_5\alpha$), R = Ac; R′ =  ; R″ = CbO*

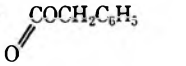
VIII ($C_5\alpha$), R = Ac; R′ = O; R″ = CbO

VIIIa ($C_5\alpha$), R = H; R′ = O; R″ = CbO

IX ($C_5\alpha$), R = H; R′ =  ; R″ = H

X ($C_5\alpha$), R = Ac; R′ =  ; R″ = CbO

XI ($C_5\alpha$), R = Ac; R′ = H_2; R″ = H

*CbO = 

(IX) is convertible to the azomethine, solacongestidine (I), in the manner described above.[10]

Thus, the conversion of solasodine to these alkaloids not only offers additional proof for the correctness of the ascribed stereochemistry and structure of these compounds but also demonstrates the utility of solasodine as a convenient starting material for their preparation.

(10) K. Schreiber and G. Adam, *Tetrahedron*, **20**, 1707 (1964).

Experimental Section[11]

O-Acetylsolasodine (IV).—*p*-Toluenesulfonic acid (12.73 g) was added portionwise to a solution of solasodine (11.95 g, 0.029 mol) in 650 ml of acetic acid while stirring at room temperature. After 2 hr a further batch of *p*-TsOH (4.25 g) was added to the reaction mixture and allowed to stand for 50 hr. The reaction product was then poured into a 1% NaCl solution (3 l.). After standing overnight the precipitate was filtered, dissolved in $CHCl_3$, and washed successively with 2% NaOH solution and water. The $CHCl_3$ extract yielded leaflets (10.99 g) from ethyl acetate: mp 189–190°[4]; $[\alpha]^{20}D$ −112.7° (c 1.81, $CHCl_3$); ir ($CHCl_3$) 3400 (NH), 1726 cm^{-1} (C=O).

Anal. Calcd for $C_{29}H_{45}NO_3$: C, 76.44; H, 9.95; N, 3.07. Found: C, 76.51; H, 9.65; N, 3.10.

O-Acetyldihydrosolasodine (V).—O-Acetylsolasodine (10.586 g, 0.023 mol) was dissolved in 550 ml of MeOH–CH_2Cl_2 (5:1) and to the solution was added 3.84 g (0.1 mol) of $NaBH_4$ while cooling. After stirring for 1 hr, ice water was added to the reaction mixture and the aqueous phase extracted twice with CH_2Cl_2. After removal of the solvent from the combined extracts, the residue crystallized as leaflets (9.251 g) from ethyl acetate: mp 211.5–213°; $[\alpha]^{20}D$ −67.13° (c 1.08, $CHCl_3$); ir (Nujol) 3280 (NH, OH), 1734 (C=O).

Anal. Calcd for $C_{29}H_{47}NO_3$: C, 76.10; H, 10.35; N, 3.06. Found: C, 75.76; H, 10.22; N, 3.28.

The mother liquor yielded a second crop (0.230 g) of V and starting material, IV (0.267 g), upon chromatography on silica gel.

O-Acetyltetrahydrosolasodine (VI).—To a suspension of 1.20 g of prereduced Pd–C (10%) catalyst in 400 ml of acetic acid was added a solution of V (9.12 g, 0.02 mol) in 100 ml of acetic acid. After the absorption of 520 ml of hydrogen in 10 hr, the uptake virtually ceased, but the hydrogenation was continued for another 10 hr. The catalyst was then removed by filtration and the filtrate was poured into 2 l. of a 2% NaCl solution.

After standing overnight the precipitate was filtered, washed with water, and dissolved in methanol. Sufficient 5% $NaHCO_3$ solution was added to the methanol until the solution was basic and the compound was taken up in ethyl acetate. Concentration of the solvent afforded 8.460 g of needles: mp 184–185°; $[\alpha]^{20}D$ −15.0° (c 1.02, $CHCl_3$); ir ($CHCl_3$) broad band centered at 3100 (OH, NH), 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{29}H_{49}NO_3$: C, 75.77; H, 10.74; N, 3.05. Found: C, 75.58; H, 10.82; N, 3.37.

N-Carbobenzoxy-O-acetyltetrahydrosolasodine (VII).—O-Acetyltetrahydrosolasodine (VI, 1.3792 g, 0.032 mol) was dissolved in 150 ml of benzene by warming. After cooling to room temperature 70 ml of $NaHCO_3$ (5%) solution and 1 g (0.6 mol) of carbobenzoxy chloride were added successively to the reaction mixture with occasional shaking. After 4 hr another 0.5-g batch of carbobenzoxychloride was added to the reaction mixture and allowed to stand overnight. The benzene layer was separated, washed repeatedly with water, dried (Na_2SO_4), and concentrated to dryness. The residue upon chromatography on a silicic acid column and elution with benzene–ethyl acetate (10:1) yielded a colorless syrup (1.5 g) which was resubmitted to silicic acid chromatography. The benzene–ethyl acetate (2:1) eluate crystallized as needles (0.9096 g) from *n*-hexane–benzene (10:1): mp 127–129°; $[\alpha]^{23}D$ −12.9° (c 1.95, $CHCl_3$); ir (Nujol) 3498 (OH), 1738 (C=O), 1677 (NC=O), 1251 cm^{-1} (COC).

Anal. Calcd for $C_{37}H_{55}NO_5$: C, 74.83; H, 9.34; N, 2.36. Found: C, 74.83; H, 9.09; N, 2.46.

In the above reaction considerable amount of insoluble matter collects at the organic and aqueous interphase. This was collected and crystallized from methanol as needles, XII (235 mg): mp 312–315° with partial sublimation at 280–290°; $[\alpha]^{20}D$ −138.9° (c 0.83, $CHCl_3$); ir (Nujol) 1731 (C=O), 1692

(11) Melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were performed by the Microanalytical Services Unit of this laboratory. Infrared spectra were obtained with a Model 421 Perkin-Elmer spectrophotometer. Optical rotations were obtained in a 1-dm tube with a Model 141 Perkin-Elmer polarimeter. Nmr spectra were determined on the Model A-60 Varian Associates spectrometer, using $CDCl_3$ as solvent with tetramethylsilane as internal standard and described in δ values (TMS, 0.0 ppm). The mass spectra in these experiments have been measured with a Hitachi Perkin-Elmer RMU-7 spectrometer. Tlc plates were precoated with silica gel G and purchased from Analtech, Inc., Wilmington, Del.

(OC=O); mass spectrum 485 (M^+, $C_{30}H_{47}O_4N$), 344, 329, 276, 274, 269.

Anal. Calcd for $C_{30}H_{47}NO_4$: C, 74.18; H, 9.75; N, 2.88. Found: C, 74.33; H, 9.75; N, 3.15.

Synthesis of Compound XII.—To a solution of O-acetyltetrahydrosolasodine (VI, 195 mg) in 20 ml of ethyl acetate was added 20 ml of 5% $NaHCO_3$ solution; the mixture was shaken. To the mixture was then added 2 ml (0.534 g) of a phosgene–benzene solution with vigorous agitation. After standing overnight, the volatile components were removed *in vacuo* and the residue crystallized from methanol as needles (57.5 mg), mp >300°. The compound exhibited an ir spectrum identical with the spectrum of XII isolated above.

N-Carbobenzoxy-O-acetyl-16-dehydrotetrahydrosolasodine (VIII).—Kiliani's chromic acid reagent (1 ml, 0.0125 mol) was added to a solution of VII (0.7897 g, 0.0013 mol) in 25 ml of acetone while stirring at 0°. Following the addition of the oxidant, the stirring was continued overnight at room temperature. Methanol (10 ml) and $NaHCO_3$ solution (20 ml, 5%) were then added to the reaction mixture and extracted with $CHCl_3$. The residue, after removal of the $CHCl_3$, was submitted to chromatography on a silica gel column. The benzene–ethyl acetate (100:1) eluate yielded lumpy crystals (564 mg) after crystallization from benzene–*n*-hexane (10:1): mp 156–158°; $[\alpha]^{20}D$ −83.3° (*c* 1.59, $CHCl_3$); ir ($CHCl_3$) 1734 (five-membered-ring ketone + acetyl), 1687 cm^{-1} (NCO).

Anal. Calcd for $C_{37}H_{53}NO_5$: C, 75.09; H, 9.03; N, 2.37. Found: C, 75.14; H, 9.08; N, 2.46.

Dihydrosolafloridine (IX). Procedure A.—Compound VIII (506 mg) dissolved in 5 ml of 2-propanol was added dropwise, in the span of 10 min, to 15 ml of boiling toluene containing 0.7 g of sodium metal. After the addition the mixture was refluxed for 3 hr. When cool, a 2 *N* HCl (100 ml) solution was added to the reaction mixture. This resulted in the collection of some insoluble matter between the organic and aqueous interphase. After its removal, the acidic solution was made alkaline with NaOH (aqueous) and extracted with ethyl acetate. The precipitate and the dried extract were combined and chromatographed on alumina. The ethyl acetate–methanol (10:1) eluate gave needles (355 mg) after crystallization from methanol. Tlc of the acetyl derivative indicated the presence of a small amount of the 16β-isomeric tetrahydrosolasodine.[12] Recrystallization of IX from methanol afforded needles: mp 280–284°; $[\alpha]^{20}D$ 24.6° (c 0.37, $CHCl_3$); ir (Nujol) broad band, centered at 3300 (OH, NH), 1050 cm^{-1} (CO).

Anal. Calcd for $C_{27}H_{47}NO_2$: C, 77.64; H, 11.34; N, 3.35. Found: C, 77.70; H, 11.05; N, 3.26.

The compound was indistinguishable from the product obtained by the reduction of solafloridine (II).

Procedure B.—Compound VIII (319.5 mg) was dissolved in 5 ml of tetrahydrofuran and added to a solution of 100 mg of lithium in 10 ml of liquid ammonia. After 5 min, 10 ml of absolute ethanol was added dropwise to the reactants. The mixture stood overnight at room temperature. Water was then added to the reaction mixture and the resulting precipitate was filtered. The filtrate was extracted with ethyl acetate and evaporated to dryness. The precipitate and the residue were combined and submitted to chromatography on alumina. Elution with ethyl acetate and crystallization from the same solvent afforded needles, mp 193–195° (110 mg). Elemental analysis and spectra showed it to be the deacetylated product of VIII, *i.e.*, N-carbobenzoxy-16-dehydrotetrahydrosolasodine (VIIIa). VIIIa possesses the following characteristics: $[\alpha]^{20}D$ −86.3° (*c* 0.87, $CHCl_3$); ir (Nujol) 3498 (OH), 1737 (five-membered-ring ketone), 1680 (NCbO), 750 cm^{-1} (monosubstituted benzene); nmr ($CDCl_3$) δ 0.65 (3 H, s, C_{18} H's), 0.87 (3 H, s, C_{19} H's), 3.67 (1 H, m, C_3 H), 5.15 (2 H, OCH_2Ph), 7.38 (5 H, s, Ar H's).

Anal. Calcd for $C_{35}H_{51}NO_4$: C, 76.46; H, 9.35; N, 2.55. Found: C, 76.72; H, 9.32; N, 2.62.

(12) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3020 (1950).

Further elution of the above chromatogram with ethyl acetate–methanol (20:1) yielded the desired dihydrosolafloridine (IX, 117.8 mg), identical in every respect with the sample obtained by procedure A.

Sodium Borohydride Reduction of VIII.—Compound VIII (110.5 mg) was dissolved in 10 ml of a solution of MeOH–CH_2Cl_2 (5:1) by warming. After cooling to room temperature, $NaBH_4$ (108.9 mg) was added with stirring to the solution and allowed to stand for 30 min. The reaction mixture was then poured into 50 ml of 5% $NaHCO_3$ solution and extracted with ethyl acetate. The residue obtained from the extract was chromatographed on silica gel. The benzene–ethyl acetate (10:1) eluate gave colorless needles (90 mg) after crystallization from hexane–benzene (10:1), mp 125–127°. The compound exhibited properties indistinguishable from authentic VII.

Preparation of Solafloridine (II).—The conversion of dihydrosolafloridine (IX) to solafloridine (II) was carried out essentially in the manner described by Schreiber and Adam.[8] Compound IX (223.5 mg) was dissolved in 25 ml of CH_2Cl_2 by warming. After the solution was cooled in an ice–salt water bath, the N-chlorosuccinimide (158.3 mg) in 10 ml of CH_2Cl_2 was added to it and the mixture allowed to stand for 1 hr. Removal of the solvent and chromatography of the residue on a silica gel column afforded the N-chlorodihydrosolafloridine (benzene–ethyl acetate eluate, 1:1) which crystallized as needles from ethanol (222 mg), mp 254–256° (lit.[8] mp *ca.* 280° dec).

Anal. Calcd for $C_{27}H_{46}NO_2Cl$: C, 71.73; H, 10.26; N, 3.09. Found: C, 71.57; H, 10.50; N, 3.00.

To a solution of sodium methylate prepared from the interaction of 70 ml of absolute methanol and 700 mg of sodium was added 401 mg of the above prepared N-chlorodihydro compound and refluxed for 2 hr in a N_2 atmosphere. The methanol was then removed *in vacuo* and water was added to the residue. The ethyl acetate extract after chromatography on alumina and elution with ethyl acetate yielded needles after two recrystallizations from ethyl acetate (79.8 mg): mp 163–164°; $[\alpha]^{20}D$ 116.0° (*c* 0.63, $CHCl_3$) [lit.[8] mp 168–170°; $[\alpha]^{20}D$ 114.8° (*c* 0.248)]. The properties (melting point, mixture melting point, and ir) of the compound were in agreement with a specimen of solafloridine[2] obtained from the natural source.

N-Carbobenzoxy-O-acetyl-16-dehydrotetrahydrosolasodine Ethylene Dithioketal (X).—Ethanedithiol (0.4 ml) and BF_3 etherate (0.4 ml) were added to a HAc (5 ml) solution of the ketone VIII (176 mg), and the reaction mixture was kept at room temperature for 3 hr with stirring. The reaction product after the usual work-up was obtained as a syrup which was submitted to chromatography over silica gel. The desired thioketal X was eluted with benzene–chloroform (3:7) and crystallized from ethanol–acetone (1:1) as needles: mp 144–146°; ir (Nujol) 1250, 1740 (OAc), 1700 cm^{-1} (NCbO).

Anal. Calcd for $C_{39}H_{57}NO_4S_2$: C, 70.13; H, 8.60; N, 2.10. Found: C, 70.41; H, 8.57; N, 2.13.

Dihydrosolacongestidine Acetate (XI).—The thioketal X (38 mg) was dissolved in absolute ethanol (10 ml) and a large excess of Raney nickel[13] suspended in ethanol was added to it. After the mixture was refluxed for 2 hr, the catalyst was filtered off and washed with chloroform. The combined catalyst washings and the filtrate yielded 19 mg of a residue which when crystallized from ether gave needles of mp 212–215°. The compound, XI, exhibited properties (melting point, mixture melting point, and ir) which were in agreement with dihydrosolacongestidine acetate[2] derived from solacongestidine of natural origin.

Registry No.—II, 2385-18-4; III, 126-17-0; IV, 6159-99-5; V, 24694-69-7; VI, 24694-70-0; VII, 24694-71-1; VIII, 24694-72-2; VIIIa, 24694-73-3; IX, 24674-74-4; X, 24694-75-5; XI, 19374-54-0; XII, 24694-77-7; N-chlorodihydrosolafloridine, 24694-78-8.

(13) No. 28 from W. R. Grace and Co., Baltimore, Md.

Autoxidation of Cholesterol *via* Hydroperoxide Intermediates[1]

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The autoxidation of cholesterol in air is shown to proceed both *via* the previously recognized photoinduced singlet oxygen attack on the A/B-ring system to give the well-known sequence of autoxidation products of cholesterol, and also by a biradical oxygen attack resulting in the formation of cholesterol 20α- and 25-hydroperoxides and their putative degradation products cholest-5-ene-3β,25-diol, cholest-5-ene-3β,20α-diol, chol-5-en-3β-ol, pregn-5-ene-3β,20α-diol, pregn-5-en-3β-ol, 3β-hydroxypregn-5-en-20-one, androst-5-ene-3β,17β-diol, androst-5-en-3β-ol, and 3β-hydroxyandrost-5-en-17-one.

As a phase of our interests in the autoxidation and metabolism of cholesterol,[2] we examined several large batches of commercial cholesterol for autoxidation products. The commonly encountered cholesterol autoxidation products 3β-hydroxycholest-5-en-7-one, cholesta-3,5-dien-7-one, cholest-5-ene-3β,7α-diol, cholest-5-ene-3β,7β-diol, and 5α-cholestane-3β,5,6β-triol were isolated or confidently detected.[3] We have established for the first time the presence in air-aged cholesterol of the putative primary product of the photoinduced singlet oxygen attack on cholesterol, 3β-hydroxy-5α-cholest-6-ene 5-hydroperoxide (**1a**),[4] and its rearrangement product, 3β-hydroxycholest-5-ene 7α-hydroperoxide (**2a**),[4d,5] from which are derived the several secondary autoxidation products mentioned above.[3d] Although titration and chromatographic data[2a,6] suggest the presence of sterol hydroperoxides in air-aged cholesterol, their specific presence in such samples has not previously been demonstrated.[7]

In addition to these autoxidation products and cholest-5-ene-3β,25-diol (**4a**),[9] we have isolated and characterized several new sterol hydroperoxides, seven known steroids not previously recognized as cholesterol autoxidation products, and chol-5-en-3β-ol (**7a**) from air-aged cholesterol. The identities of the seven known steroids cholest-5-ene-3β,20α-diol (**6a**), pregn-5-ene-3β,20α-diol (**9a**), pregn-5-en-3β-ol (**8a**), 3β-hydroxypregn-5-en-20-one (**10a**), androst-5-ene-3β,17β-diol (**12a**), androst-5-en-3β-ol (**11a**), and 3β-hydroxyandrost-5-en-17-one (**13a**) were established by direct comparisons of the steroid recovered from air-aged cholesterol with an authentic sample.

The structure of the cholane derivative **7a**, surmised from chromatographic and color-test behavior, infrared absorption spectra, and formation of a monoacetate **7b**, was confirmed by synthesis. Chol-5-ene-3β,24-diol (**7c**) was selectively converted to the 24-mono-*p*-toluenesulfonate (**7d**) which was reduced by lithium aluminum hydride to the required 24-deoxy steroid chol-5-en-3β-ol, identical with the suspected sample obtained from air-aged cholesterol.

The structure of 3β-hydroxycholest-5-ene 25-hydroperoxide (**3a**), that sterol hydroperoxide isolated from air-aged cholesterol in best yield (0.1–1%), was established by elemental analysis, formation of a diacetate **3b**,[10] reduction by sodium borohydride to the known cholest-5-ene-3β,25-diol (**4a**), positive peroxide color tests, and infrared absorption showing two strong OH stretching bands at 3620 and 3560 cm^{-1} characteristic of the hydroxyl and hydroperoxyl groups, respectively. Proton spectra of the diacetate **3b** showing the C_{26}- and C_{27}-methyl protons as a six-proton singlet at 1.28 ppm, deshielded 0.41 ppm by the 25-peracetoxyl group, complete the proof.[11]

A second sterol hydroperoxide 3β-hydroxycholest-5-ene 20α-hydroperoxide (**5a**) was similarly identified, with formation of a diacetate **5b** and sodium borohydride reduction to the known cholest-5-ene-3β,20α-diol (**6a**), positive peroxide color tests, characteristic absorption at 3620 and 3560 cm^{-1}, and proton spectra supporting the assigned structure. The C_{18}- and C_{21}-methyl group proton signals in the diacetate **5b** were singlets deshielded 0.18 and 0.41 ppm, respectively, by the 20α-peracetoxyl group.[12]

Other, as yet unidentified, sterol hydroperoxides X_1, X_2, and X_3 have been isolated and partially characterized. The structure of X_1, isolated in poor yield (0.002%) and separated from **3a** only with difficulty, as

(1) (a) Paper VII of the series "Sterol Metabolism." Paper VI: L. L. Smith and R. E. Gouron, *Water Res.*, **3**, 141 (1969). (b) Presented in part at the 5th International Symposium on the Chemistry of Natural Products, London, July 8–13, 1968, Abstracts, p 360, and before the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 8–13, 1968, ORGN 58. (c) Supported financially by a grant from the U. S. Public Health Service (HE-10160).

(2) (a) L. L. Smith, W. S. Matthews, J. C. Price, R. C. Bachmann, and B. Reynolds, *J. Chromatogr.*, **27**, 187 (1967); (b) J. E. van Lier and L. L. Smith, *Biochemistry*, **6**, 3269 (1967); (c) J. E. van Lier and L. L. Smith, *Anal. Biochem.*, **24**, 419 (1968).

(3) For a review of steroids formed from cholesterol by autoxidation see (a) S. Bergström, *Ark. Kemi, Mineral., Geol.*, **16A**, No. 10, 1 (1942); (b) S. Bergström and B. Samuelsson in "Autoxidation and Antioxidants," Vol. 1, W. O. Lundberg, Ed., Interscience Publishers, New York, N. Y., 1961, pp 233–248; (c) L. F. Fieser and M. Fieser "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 233–237; (d) P. Bladon in "Cholesterol, Chemistry, Biochemistry, and Pathology," R. P. Cook, Ed., Academic Press, Inc., New York, N. Y., 1958, pp 76–77.

(4) (a) G. O. Schenck, K. Gollnick, and O.-A. Neumüller, *Justus Liebigs Ann. Chem.*, **603**, 46 (1957); (b) G. O. Schenck and O.-A. Neumüller, *ibid.*, **618**, 194 (1958); (c) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961); (d) E. Caspi, J. B. Greig, P. J. Raum, and K. R. Varma, *Tetrahedron Lett.*, 3829 (1968).

(5) (a) G. O. Schenck, O.-A. Neumüller, and W. Eisfeld, *Angew. Chem.*, **70**, 595 (1958); (b) G. O. Schenck, O.-A. Neumüller, and W. Eisfeld, *Justus Liebigs Ann. Chem.*, **618**, 202 (1958); (c) B. Lythgoe and S. Trippett, *J. Chem. Soc.*, 471 (1959).

(6) (a) J. A. Fioriti and R. J. Sims, *J. Amer. Oil Chem. Soc.*, **44**, 221 (1967); (b) F. Neuwald and K.-E. Fetting, *Pharm. Ztg.*, **108**, 1490 (1963); (c) C. Horvath, *J. Chromatogr.*, **22**, 52 (1966).

(7) Sterol hydroperoxides have been demonstrated chromatographically in irradiated eggs[6a] and in formalinized human brain[6b] as artifacts. A stigmasterol hydroperoxide has been isolated from chestnut leaves under conditions which suggest that sterol hydroperoxides may occur in nature.[6c]

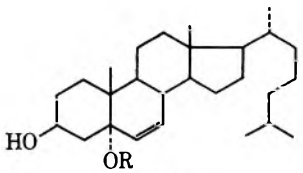
(8) (a) L. Acker and H. Greve, *Fette, Seifen, Anstrichm.*, **66**, 1009 (1963); (b) J. E. van Lier and L. L. Smith, *Tex. Rep. Biol. Med.*, **27**, 167 (1969); (c) F. G. Fischer and H. Mägerlin, *Justus Liebigs Ann. Chem.*, **636**, 88 (1960).

(9) (a) L. F. Fieser, W.-Y. Huang, and B. K. Bhattacharyya, *J. Org. Chem.*, **22**, 1380 (1957); (b) A. L. J. Beckwith, *Proc. Chem. Soc.*, 194 (1958).

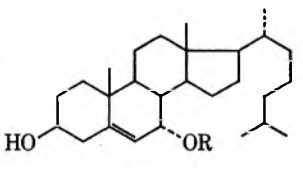
(10) Tertiary hydroperoxides are readily acetylated in distinction to tertiary alcohols; *cf.* E. L. Shapiro, T. Legatt, and E. P. Oliveto, *Tetrahedron Lett.*, 663 (1964).

(11) Compare deshielding of 0.56 ppm in **4b** by the 25-acetoxyl group which also reduces the normal doublet character of the C_{26}- and C_{27}-methyl proton signal in cholesterol to a singlet.

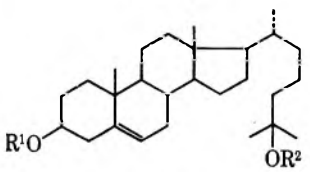
(12) Compare deshielding of 0.13 and 0.30 ppm, respectively, by the 20α-hydroxyl group in cholest 5-ene-3β,20α-diol; *cf.* A. Mijares, D. I. Cargill, J. A. Glasel, and S. Lieberman, *J. Org. Chem.*, **32**, 810 (1967).



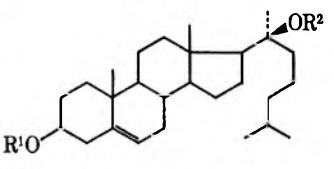
1a, R = OH
b, R = H



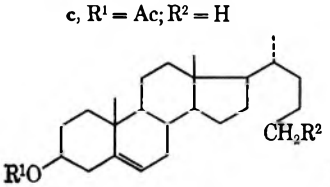
2a, R = OH
b, R = H



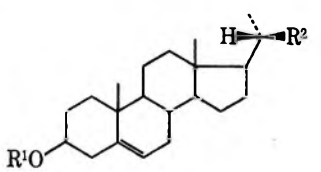
3a, $R^1 = H$; $R^2 = OH$
b, $R^1 = Ac$; $R^2 = OAc$
4a, $R^1 = R^2 = H$
b, $R^1 = R^2 = Ac$
c, $R^1 = Ac$; $R^2 = H$



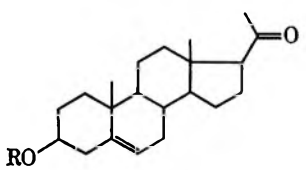
5a, $R^1 = H$; $R^2 = OH$
b, $R^1 = Ac$; $R^2 = OAc$
6a, $R^1 = R^2 = H$
b, $R^1 = Ac$; $R^2 = H$



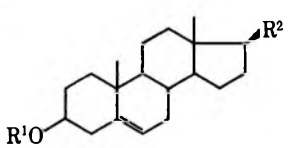
7a, $R^1 = R^2 = H$
b, $R^1 = Ac$; $R^2 = H$
c, $R^1 = H$; $R^2 = OH$
d, $R^1 = H$; $R^2 = OTs$



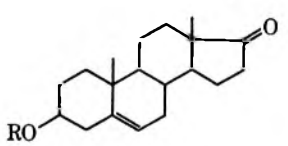
8a, $R^1 = R^2 = H$
b, $R^1 = Ac$; $R^2 = H$
9a, $R^1 = H$; $R^2 = OH$
b, $R^1 = Ac$; $R^2 = OAc$



10a, R = H
b, R = Ac



11a, $R^1 = R^2 = H$
b, $R^1 = Ac$; $R^2 = H$
12a, $R^1 = H$; $R^2 = OH$
b, $R^1 = Ac$; $R^2 = OAc$



13a, R = H
b, R = Ac

a cholesterol hydroperoxide was supported by high resolution mass measurement, positive peroxide color tests, strong absorption at 3620 and 3560 cm^{-1}, and sodium borohydride reduction to a new sterol diol not as yet identified. However, this sterol diol is not identical with the recently prepared cholest-5-ene-3β,17α-diol[13] or with 20-isocholest-5-ene-3β,20β-diol,[12] thus ruling out prospective 17α- or 20-iso-20β-hydroperoxide structures for X_1. Amounts of the other sterol hydroperoxides X_2 and X_3 obtained were inadequate for further chemical studies.

The presently observed autoxidation of cholesterol in the side chain is in clear distinction to previously described photoinduced singlet oxygen oxidation of cholesterol in the A/B ring system. Formation of the tertiary hydroperoxides **5a** and **3a** suggests that the autoxidative process involved is that of biradical oxygen attack at the preferred tertiary 20α- and 25-carbon atoms. In the same manner postulated for the decomposition of the 7α-hydroperoxide of cholesterol to give 7α- and 7β-hydroxy- and 7-oxo derivatives,[3d] so the decomposition of the 20α- and 25-hydroperoxides might be predicted to yield related tertiary alcohol and degraded ketone derivatives.

The 3β,25-diol **4a** already recognized as an autoxidation product of cholesterol[9] must be derived from the 25-hydroperoxide **3a**. Homolysis of the peroxide oxygen–oxygen bond and combination of the 25-alkoxy radical thereby produced with a hydrogen radical would afford the 3β,25-diol. A similar argument may be advanced to account for the presence of the 3β,20α-diol **6a** in air-aged cholesterol, by homolysis of the 20α-hydroperoxide oxygen–oxygen bond and combination with a hydrogen radical.

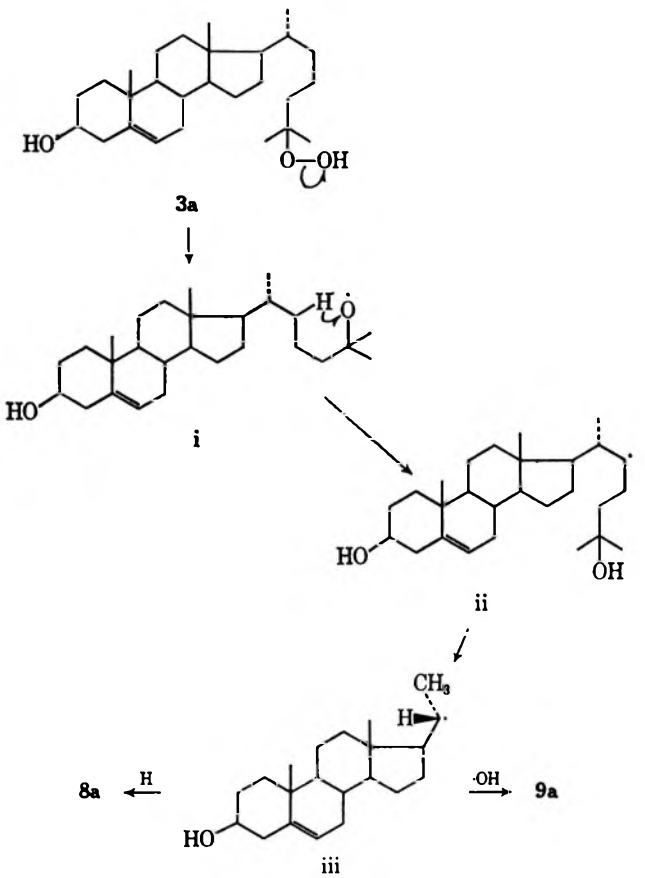
The degraded steroids **7a**, **8a**, **9a**, **10a**, **11a**, and **12a** may be derived from the 20α- and 25-hydroperoxides **5a** and **3a** by characteristic bond cleavage reactions involving radical intermediates. Thus, the 25-alkoxy radical obtained from the 25-hydroperoxide **3a** by homolysis, on β scission of the C_{25}–C_{26} bond, might yield 3β-hydroxy-27-norcholest-5-en-25-one, a product not detected in air-aged cholesterol in our studies despite a search for it. However, β scission of the C_{24}–C_{25} bond leading to a cholene 24 radical could then result by combination with a hydrogen radical in the formation of chol-5-en-3β-ol, which product was indeed isolated from air-aged cholesterol.

In the case of the 20α-hydroperoxide **5a**, β scission of the C_{20}–C_{22} bond in the 20α-alkoxy radical derived from **5a** by homolysis should result in formation of the 20 ketone **10a**, which product was isolated in our experiments. The presence of the 17 ketone **13a** in air-aged cholesterol may be accounted for by a similar sequence of radical reactions on a postulated cholesterol 17α-hydroperoxide not isolated in our present work.[14]

Scission of the C_{17}–C_{20} bond of the 20α-alkoxy radical derived from the 20α-hydroperoxide **5a** would give a 17 radical which on combination with a hydrogen radical would lead to androst-5-en-3β-ol, and with a hydroxyl radical would give the 3β,17β-diol **12a**. Both androstane derivatives were found in air-aged cholesterol. The similarly related pregnanes **8a** and **9a** may be viewed as originating from the 25-alkoxy radical initially formed from the 25-hydroperoxide **3a**, with a 1,5 migration of a 22 hydrogen *via* a cyclic transition state to yield a 25-hydroxy 22 radical which undergoes scission of the C_{20}–C_{22} bond to yield a pregnane 20 radical and the fragment 2-methylpent-4-en-2-ol. The 20 radical would afford pregn-5-en-3β-ol on combination with a hydrogen radical, the 3β,20α-diol **9a** on combination with a hydroxyl radical. Notably, no pregn-5-ene-3β,20β-diol was detected in our search of air-aged cholesterol. Accordingly, the 20-radical obtained on scission of the C_{20}–C_{22} bond retains configuration long enough for stereospecific recombination with hydroxyl radicals to give **9a**. In support of this formulation we have detected by gas chromatography and mass spectrometry the postulated fragment 2-

(13) N. K. Chaudhuri, R. Nicholson, and M. Gut, Abstracts of Papers, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 7–12, 1969.

(14) Cooccurrence of pregnane 17α-hydroperoxides and related 17 ketones derived therefrom has been noted; *cf.* W. P. Schneider and D. A. Ayer, Proceedings of the 2nd International Congress on Steroid Hormones. Milan, May 23–28, 1966, Excerpta Medica Foundation, Amsterdam, 1967, pp 254–260.



methylpent-4-en-2-ol in odorous material condensed from air-aged cholesterol.

The presence of androstane, pregnane, and cholane derivatives in air-aged cholesterol has not been noted heretofore. Examination of commercial cholesterol of recent manufacture or of purified cholesterol for these derivatives was without success. The controlled production of the hydroperoxides **3a** and **5a** in high-purity cholesterol heated in air can be observed chromatographically, and the concomitant formation of the degraded steroids may also be observed in such samples. We regard these observations as strong evidence that the degraded androstane, pregnane, and cholane derivatives isolated from air-aged cholesterol be derived from the 20α- and 25-hydroperoxides **5a** and **3a** formed in turn by biradical attack of triplet oxygen on cholesterol in the solid state.

Experimental Section[15]

Cholesterol Samples.—Initial isolation work was done with a lot of cholesterol distributed by Pfanstiehl Laboratories, Waukegan, Ill. (lot 1669, mp 147–148° at time of manufacture in 1947 by Wilson Laboratories, Chicago, Ill.), obtained as 10-g samples in unopened original brown glass vials sealed with cork and wax at manufacture, thus of an authenticated age of 20 years. Other commercial lots were used for additional isolation work to secure larger amounts of products. Highly purified cholesterol heated as a thin layer in an oven in the dark at 100° for 7 days afforded accelerated formation of the sterol hydroperoxides and the characteristic degradation products. The hydroperoxides **3a** and **5a** and associated degradation products could be detected in such pure cholesterol after 2 days of heating. At this point thin layer chromatograms of air-heated cholesterol resembled in detail the chromatograms of naturally air-aged cholesterol.[17] Prolonged heating led to increased difficulties in fractionation and to lower yields of the sterol hydroperoxides. The best hydroperoxide yields were obtained after heating pure cholesterol for 5–7 days with recrystallization of the oxidized batch from methanol and recovery of the oxidation products in the methanol mother liquor. The pure cholesterol was again subjected to heating for 5–7 days and recrystallization from methanol. The methanol mother liquors from five such 5–7-day heating periods were combined for fractionation. Yields of the hydroperoxides **3a** and **5a** varied in these heating experiments between 0.001 and 0.1%, with the 25-hydroperoxide **3a** predominating over **5a** and other hydroperoxides by a 10–100-fold factor.

Fractionation Procedure.—Batches of air-aged cholesterol (10–1000 g) were repeatedly recrystallized from methanol so as to give cholesterol and methanol mother liquors containing the autoxidation products. Exposure to light and air was minimized during all phases of fractionation, and thin layer chromatographic monitoring at each step suggested that the composition of autoxidation products was not altered appreciably. The autoxidation products were partitioned between methanol–hexane to remove apolar material (19% by weight, containing cholesta-3,5-dien-7-one) and diethyl ether–0.1 *N* sodium hydroxide solution to remove acidic material (16% by weight). The thoroughly washed and dried ether solution was evaporated under vacuum to yield a mobile oil enriched in autoxidation products of our interest.

Chromatography on silica gel using benzene–ethyl acetate gave select fractions containing **1a**, **3a**, **5a**, X_1, **4a**, **6a**, **7a**, **8a**, **9a**, **10a**, **11a**, **12a**, and **13a**, free from polar sterols (**2b**, *etc.*) but still containing cholesterol. Fractional crystallization from benzene

(15) Melting points were taken on a calibrated Kofler block under microscopic magnification. Optical rotations were obtained on 0.5–1% solutions in chloroform. Infrared absorption spectra were recorded over the range of 400–4000 cm^{-1} with a Perkin-Elmer Model 337 spectrophotometer equipped with a beam condenser, using 1.5-mm-diameter potassium bromide disks or as 0.003 *M* solutions in carbon tetrachloride (1-mm path). Proton spectra were recorded on 15% solutions in deuteriochloroform using a Varian Instruments Model A-60A spectrometer. Chemical shifts were recorded in parts per million downfield from an internal reference of tetramethylsilane. High-resolution mass spectra were obtained on a CEC Model 21-110B mass spectrometer, medium-resolution mass spectra on an LKB-9000 mass spectrometer. Elemental analyses were performed by the Huffman Laboratories, Wheatridge, Colo.

Ascending thin layer chromatography was conducted with benzene–ethyl acetate (3:2) on silica gel HF_{254} chromatoplates using techniques previously described.[2a] Visualization of steroids was by means of 50% aqueous sulfuric acid spray. Gas chromatography was conducted on 3% SE-30 and 3% QF-1 columns by means already described.[2b,c] Preparative gas chromatography on 3% QF-1 columns[16a] and column chromatography on Sephadex LH-20[16b] (Pharmacia Fine Chemicals Inc., Uppsala) were conducted as described elsewhere in detail. Chromatographic behavior for steroids is given in the order: thin layer mobility in benzene–ethyl acetate (3:2) as R_C values with cholesterol as unit mobility; color response to 50% sulfuric acid, in parentheses; relative retention times (r_T) on 3% QF-1 and on 3% SE-30, with cholesterol serving as unity.

(16) (a) J. E. van Lier and L. L. Smith, *J. Chromatogr.*, **36**, 7 (1968); (b) J. E. van Lier and L. L. Smith, *ibid.*, **41**, 37 (1969).

(17) Very complex thin layer chromatograms result.[2a,8c] Sterol hydroperoxides are not resolved as a group on such chromatograms but are recognized among other steroid products by selective response to both potassium iodide–starch and ferrous thiocyanate color tests for peroxides.[18] Color responses to 50% sulfuric acid were not sufficiently distinctive for confident recognition of the hydroperoxides in mixtures. As an adjunct means of recognition of sterol hydroperoxides on thin layer chromatograms a 2–10-μg sample of mixed sterols was spotted as usual, and 5 μl of a freshly prepared 1% solution of sodium borohydride in methanol was carefully spotted directly over the sample spot. After the methanol evaporated the chromatoplate was irrigated as usual with benzene–ethyl acetate (3:2) and visualized with 50% sulfuric acid. Careful comparison of the borohydride reduced chromatograms *vs.* the same sample not reduced before irrigation permitted recognition of a change in mobility and of color-test response for the sterol hydroperoxides, whose mobilities after reduction matched identically those of the known hydroxylated cholesterol reference samples. Although the sterol hydroperoxides **3a**, **5a**, X_1, and X_2 are not well resolved from one another on adsorption mode thin layer chromatograms, the reduced derivatives **4a** and **6a** and the alcohol derived from X_1 are readily resolved thereby, thus permitting direct thin layer chromatographic analysis of the composition of a given mixture of sterol hydroperoxides containing **3a**, **5a**, and X_1. Thin layer chromatographic mobility and color response to sulfuric acid characterize the hydroperoxides and their respective borohydride reduction products as follows: **1a**, 0.59 (green-blue); **2a**, 0.64 (green-blue); **3a**, 0.84 (brown-red); **5a**, 0.93 (gray-brown); X_1, 0.95 (gray-brown); X_2, 0.82 (gray-brown); X_3, 0.62 (brown-red); **1b**, 0.35 (sky blue); **2b**, 0.22 (sky blue); cholest-5-ene-3β,7β-diol, 0.27 (sky blue); **4a**, 0.57 (purple-blue); **6a**, 0.88 (green-blue); X_1 alcohol, 0.77 (red-brown); X_2 alcohol, 0.74 (green-blue); X_3 alcohol, 0.24 (gray-brown).

(18) D. Waldi in "Thin-Layer Chromatography, A Laboratory Handbook," E. Stahl, Ed., Springer-Verlag, Berlin, 1965, pp 483–502.

removed cholesterol and afforded 6 g of **4a** (from 1 kg of air-aged cholesterol). Rechromatography of the benzene mother liquors of silica gel with benzene–ethyl acetate gave a more mobile fraction containing the steroids of our interest and a more polar fraction containing the 5α-hydroperoxide **1a**, **4a**, **9a**, and **12a**.

3β-Hydroxy-5α-cholest-6-ene 5-Hydroperoxide (1a) and 3β-Hydroxycholest-5-ene 7α-Hydroperoxide (2a).—The more polar sterol fraction was shown to contain **1a** by thin layer chromatography, both by direct observation and by the borohydride reduction procedure. Gas chromatography showed cracking patterns characteristic of authentic **1a** (peaks at r_T 0.53 and 0.47 on 3% QF-1). The fraction was chromatographed on Sephadex LH-20 in neat methylene chloride, but the hydroperoxide recovered was **2a**, recrystallized from hexane–diethyl ether, mp 154–158° dec (lit. mp 154° dec,[5a] 154–155° dec,[5c] 154–156.5° dec,[5b] 154–156°[4d]); $\tilde{\nu}_{max}^{KBr}$ 3400, 1620, 1050 cm^{-1}, different from spectra of **1a**. Gas chromatography gave a decomposition pattern characteristic of authentic **2a** (r_T 0.47 and 4.70, due to 3β-hydroxycholest-5-en-7-one). Authentic **1a** [mp 149–151° dec (lit. mp 142° dec,[4a] 148–149° dec,[4b] 145–148° dec,[5b] 149.5–150.5°,[4c] 147–149°[4d]); $\tilde{\nu}_{max}^{KBr}$ 3400, 3200, 1620, 1040, 1020 cm^{-1}] subjected to similar chromatography was completely isomerized to **2a**, mp 154–158°.

Chromatography on Sephadex LH-20.—The more mobile fraction containing autoxidation products of our interest was chromatographed with methylene chloride–acetone (9:1) on Sephadex LH-20,[16b] a key procedure in the resolution of the hydroperoxides. Group fractions obtained in order were (A) cholesterol, monohydroxy steroids (**7a**, **8a**, **11a**), and hydroxy ketones (**10a**, **13a**), together with the 3β,20α-diol **6a**; (B) the polar diol fraction (**4a**, **9a**, **12a**); and (C) the substantially retarded hydroperoxide fraction (**3a**, **5a**, X_1, X_2, X_3).

After fractional crystallization of more cholesterol from the A fraction the material was subjected to Girard T separation.[19] From the ketonic fraction after preparative thin layer chromatography using benzene–ethyl acetate (3:2) there was isolated the two ketones, **10a** and **13a**.

3β-Hydroxypregn-5-en-20-one (10a).—Material from the more mobile band from the preparative thin layer chromatogram was eluted with methanol–chloroform (1:2) and recrystallized from hexane–diethyl ether to give **10a**, 12 mg, mp 191–192°, not depressed on admixture with an authentic sample (lit.[20] mp 188–194°); $\tilde{\nu}_{max}^{KBr}$ 3420, 1690, 1620, 1060 cm^{-1}; R_C 0.74 (red-orange); r_T 0.97, 0.33; identical in these properties with authentic **10a**.

Acetylation with acetic anhydride–pyridine in the usual manner gave the monoacetate **10b**, mp 145.0–145.5°, not depressed on admixture with authentic **10b** (lit.[20] mp 145–150°); $\tilde{\nu}_{max}^{KBr}$ 1720, 1690, 1620, 1240, 1030 cm^{-1}; R_C 1.42 (red-orange); r_T 1.50, 0.49; identical in all respects with authentic **10b**.

3β-Hydroxyandrost-5-en-17-one (13a).—The more polar component from the Girard ketonic fraction eluted from the thin layer chromatoplate with methanol–chloroform (1:2) was recovered by preparative gas chromatography. Only a very small amount of this sample could be obtained, mp 125° (lit.[20] mp 145–150°), and further purification to a satisfactory melting point could not be achieved. Authentic **13a** subjected to preparative gas chromatography on 3% QF-1 in the same manner likewise exhibited the characteristic, depressed melting point. Identity of the sample was assured on other criteria: $\tilde{\nu}_{max}^{KBr}$ 3420, 1740, 1730, 1620, 1060 cm^{-1}; R_C 0.65 (purple red); r_T 0.75, 0.21; identical in these properties with authentic **13a**.

Acetylation of the material with acetic anhydride–pyridine in the usual manner gave a product recovered by gas chromatography and crystallized from chloroform, identified as the monoacetate **13b**, mp 165–170° (lit.[20] mp 168–172°); $\tilde{\nu}_{max}^{KBr}$ 1730, 1740, 1745, 1620, 1240, 1020 cm^{-1}; R_C 1.26 (purple-red); r_T 1.16, 0.30; identical in these properties with authentic **13b**.

The Girard nonketonic fraction was chromatographed on a 2-mm thick silica gel PF_{254} chromatoplate to resolve the alcohols **7a**, **8a**, and **11a** with mobility of cholesterol from the diol **6a**. The mixed alcohols were eluted together and resolved by gas chromatography on 3% QF-1, giving chromatographically pure preparations but with melting points some 5–10° below those of authentic samples.

Androst-5-en-3β-ol (11a).—The first-eluted alcohol **11a** was rechromatographed on 3% QF-1 and identified by spectral and chromatographic data: $\tilde{\nu}_{max}^{KBr}$ 3400, 1620, 1050 cm^{-1}; R_C 0.98 (magenta); r_T 0.21, 0.10; identical in these properties with authentic **11a**, mp 130–134° (lit.[20] mp 131°), prepared by lithium aluminum hydride reduction of 3β-acetoxyandrost-5-en-17β-ol *p*-toluenesulfonate.

Acetylation of **11a** with acetic anhydride–pyridine in the usual fashion with purification by preparative gas chromatography, gave the monoacetate, crystallized from chloroform to give pure **11b**, mp 89–92°, not depressed on admixture with authentic **11b**, mp 90–92° (lit.[20] mp 91–93°); $\tilde{\nu}_{max}^{KBr}$ 1730, 1620, 1240, 1030 cm^{-1}; R_C 1.55 (magenta); r_T 0.31, 0.16; identical in these properties with authentic **11b**.

Pregn-5-en-3β-ol (8a).—The middle component resolved on 3% QF-1 gas chromatographic columns of mixtures of **11a**, **8a**, and **7a** was the alcohol **8a**, crystallized from diethyl ether; $\tilde{\nu}_{max}^{KBr}$ 3400, 1620, 1050 cm^{-1}; R_C 0.96 (magenta); r_T 0.31, 0.21; identical in these properties with authentic **8a**, mp 135–136° (lit[20] mp 134–136°), prepared by lithium aluminum hydride reduction of the 20α-*p*-toluenesulfonate 3β-acetate diester of **9a**.

Acetylation of **8a** isolated from air-aged cholesterol with acetic anhydride–pyridine in the usual manner, followed by purification by preparative gas chromatography and recrystallization from chloroform, gave the 3β-monoacetate **8b**, mp 147–148°, not depressed on admixture with authentic **8b**, mp 148–150° (lit.[20] mp 147–150°); $\tilde{\nu}_{max}^{KBr}$ 1730, 1620, 1240, 1030 cm^{-1}; R_C 1.56 (magenta); r_T 0.52, 0.29; identical in these properties with authentic **8b**.

Chol-5-en-3β-ol (7a). (A) From Air-Aged Cholesterol.—The third component effluxed from the preparative gas chromatogram of the mixture of **11a**, **8a**, and **7a** was **7a**, crystallized from diethyl ether, mp 120–125°, depressed from gas chromatography; $\tilde{\nu}_{max}^{KBr}$ 3400, 1620, 1060, 1040 cm^{-1}; R_C 1.00 (magenta); r_T 0.62, 0.47; identical in these properties with authentic **7a** prepared under (B) below.

(B) From 3β-Acetoxychol-5-enic Acid.—A solution of 2 g of 3β-acetoxychol-5-enic acid in diethyl ether was refluxed overnight with excess lithium aluminum hydride. The mixture was poured onto ice, acidified with 50% hydrochloric acid, and extracted twice with 100-ml portions of diethyl ether. The pooled ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated under vacuum. Crystallization of the residue from ethyl acetate gave 1.2 g of the 3β,24-diol **7c**, mp 194–196° (lit.[20] mp 193–195°). A solution of 10 g of **7c** in 25 ml of dry pyridine at 0° was treated with 5 g of *p*-toluenesulfonyl chloride. The progress of the reaction was monitored by thin layer chromatography and the reaction was terminated by pouring into ice when about half complete. The precipitate obtained was filtered, washed with water, dried under vacuum, and redissolved in diethyl ether. Without separating the 3β,24-diol **7c** and the 24-mono-*p*-toluenesulfonate **7d**, the reaction mixture was refluxed overnight with excess lithium aluminum hydride and worked up in the manner described above, yielding a mixture of **7a** and **7c**. After chromatography on silica gel using hexane–diethyl ether (7:3), there was obtained 160 mg of pure **7a**, mp 127–130°; $\tilde{\nu}_{max}^{KBr}$ 3400, 1620, 1060, 1040 cm^{-1}; R_C 1.00 (magenta); r_T 0.62, 0.47.

Anal. Calcd for $C_{24}H_{40}O$ (344.56): C, 83.66; H, 11.70. Found: C, 83.60; H, 11.83.

Chol-5-en-3β-ol 3β-Acetate (7b). (A) From Air-Aged Cholesterol.—The sample of **7a** recovered from air-aged cholesterol was acetylated with acetic anhydride–pyridine in the usual manner to give the monoacetate **7b**, recrystallized from chloroform, mp 125–128°, not depressed on admixture with authentic **7b**; $\tilde{\nu}_{max}^{KBr}$ 1725, 1620, 1250, 1040 cm^{-1}; R_C 1.57 (magenta); r_T 1.16, 0.70; identical in all respects with authentic **7b**.

(B) From Synthesis.—Acetylation of **7a** derived by synthesis with acetic anhydride in the usual fashion gave an acetylated product which after chromatography on silica gel was recrystallized from methanol, yielding 40 mg of pure **7b**, mp 127–129°; $\tilde{\nu}_{max}^{KBr}$ 1725, 1620, 1250, 1040 cm^{-1}; R_C 1.57 (magenta); r_T 1.16, 0.70.

Anal. Calcd for $C_{26}H_{42}O_2$ (386.60): C, 80.77; H, 10.95. Found: C, 80.86; H, 10.78.

Cholest-5-ene-3β,20α-diol (6a). (A) From Air-Aged Cholesterol.—The second, less mobile band on the preparative thin layer chromatogram of the nonketone fraction from which **11a**, **8a**, and **7a** had been isolated gave the 3β,20α-diol **6a** on rechromatography, crystallized from hexane–ethyl acetate; $\tilde{\nu}_{max}^{KBr}$ 3400,

(19) J. J. Schneider, *J. Biol. Chem.*, **183**, 365 (1950); **194**, 337 (1952).

(20) Melting points of well-known steroids are taken from the compendium, J. Jacques, H. Kagan, G. Ourisson, "Selected Constants, Optical Rotatory Power. Ia. Steroids," Vol. 14 of "Tables of Constants and Numerical Data," S. Allard, Ed., Pergamon Press, Oxford, 1965.

1620, 1060 cm^{-1}; R_C 0.93 (green-blue); r_T 2.09, 1.56; identical in these properties with authentic **6a**. A sample of the 20α-hydroperoxide **5a** reduced in methanol with sodium borohydride also gave the 3β,20α-diol **6a**, identified by spectral and chromatographic properties with authentic **6a**.

Acetylation of **6a** derived from air-aged cholesterol and of **6a** derived by borohydride reduction of **5a** with acetic anhydride–pyridine in the usual manner gave the 3β-monoacetate **6b**, purified by gas chromatography. mp 153–157°, not depressed on admixture with authentic **6b** (lit.[20] mp 156–157°); $\tilde{\nu}_{max}^{KBr}$ 3570, 1720, 1620, 1260, 1030 cm^{-1}; R_C 1.40 (green-blue); r_T 3.00, 2.21; identical in all respects with authentic **6b**.

Cholest-5-ene-3β,25-diol (4a).—The diol fraction (B) from the Sephadex LH-20 column contained **4a**, **9a**, and **12a** together with unidentified components. Fractional crystallization of the mixture from ethyl acetate gave **4a**, mp 172–176°, not depressed on admixture with authentic **4a** (lit.[20] mp 172–183°); $\tilde{\nu}_{max}^{KBr}$ 3330, 1620, 1060 cm^{-1}; R_C 0.57 (purple-blue); r_T 2.38, 1.64; identical in these properties with authentic **4a**. The total yield of **4a** from this and other fractions was 15 g/kg of air-aged cholesterol.

Reduction of **3a** (50 mg) in methanol by sodium borohydride gave **4a** (28 mg), mp 180.5–181.5°, not depressed on admixture with authentic **4a**, identical by spectral and chromatographic comparison with authentic **4a**.

Acetylation of 10 mg of **4a** from air-aged cholesterol with acetic anhydride–pyridine in the usual manner gave the 3β-monoacetate **4c**, mp 139–140°, not depressed on admixture with authentic **4c** (lit.[20] mp 138–142°); $\tilde{\nu}_{max}^{KBr}$ 3450, 1730, 1620, 1250, 1030 cm^{-1}; R_C 1.11 (purple-red); r_T 3.82, 2.32; identical in all respects with authentic **4c**. A sample of **4c**, mp 139–140°, derived from **3a**, was similarly identified by spectral and chromatographic data.

Pregn-5-ene-3β,20α-diol (9a).—The mother liquor remaining after crystallization of **4a** was chromatographed on Sephadex LH-20 and the fractions containing **9a** still contaminated with **4a** were resolved on thin layer chromatoplates using benzene–ethyl acetate (3:2), thus yielding **9a**, 8 mg, crystallized from ethyl acetate, mp 183–184°, not depressed on admixture with authentic **9a** (lit.[20] mp 177–184°); $\tilde{\nu}_{max}^{KBr}$ 3400, 1620, 1050 cm^{-1}; R_C 0.41 (red-purple); r_T 0.72, 0.38; identical in all respects with authentic **9a**.

Acetylation of **9a** with acetic anhydride–pyridine in the usual manner gave the diacetate **9b**, purified by additional thin layer and gas chromatography, mp 143–144°, not depressed on admixture with an authentic sample of **9b** (lit.[20] mp 142–147°); $\tilde{\nu}_{max}^{KBr}$ 1730, 1620, 1250, 1030 cm^{-1}; R_C 1.44 (red-purple); r_T 1.74, 0.74; identical in all respects with authentic **9b**.

Androst-5-ene-3β,17β-diol (12a).—The 3β,17β-diol **12a** was eluted after **9a** from the Sephadex LH-20 column of the diol fraction (B). After thin layer chromatography and recrystallization from ethyl acetate and from hexane–ethyl acetate the pure sample was obtained, mp 178–179°, not depressed on admixture with authentic **12a** (lit.[20] mp 174–184); $\tilde{\nu}_{max}^{KBr}$ 3400, 1620, 1050 cm^{-1}; R_C 0.41 (red-purple); r_T 0.44, 0.22; identical in all respects with authentic **12a**.

Acetylation of **12a** with acetic anhydride in the usual manner gave the 3β,17β-diacetate **12b**, mp 158.0–159.5°, not depressed on admixture with authentic **12b** (lit.[20] mp 156–158°); $\tilde{\nu}_{max}^{KBr}$ 1730, 1620, 1250, 1040 cm^{-1}; R_C 1.32 (red-purple); r_T 1.13, 0.45; identical in all respects with authentic **12b**.

3β-Hydroxycholest-5-ene 25-Hydroperoxide (3a).—The retarded hydroperoxide fraction (C) from the key Sephadex LH-20 chromatographic column contained **3a**, **5a**, X_1, X_2, and X_3. Crystallization of the hydroperoxide fraction from ethyl acetate afforded 1.2 g of **3a** (from 1 kg of aged cholesterol), mp 157–158°; $[\alpha]_D$ −39° (*c* 0.94); $\tilde{\nu}_{max}^{KBr}$ 3400, 3270 (shoulder), 3180 (shoulder), 1630, 1050 cm^{-1}; $\tilde{\nu}_{max}^{CCl_4}$ 3620 (hydroxyl), 3560 (hydroperoxyl) cm^{-1}; R_C 0.84 (brown-red).

Anal. Calcd for $C_{27}H_{46}O_3$ (418.63); C, 77.46; H, 11.07. Found: C, 77.36; H, 11.22.

3β-Acetoxycholest-5-ene 25-Hydroperoxide 25-Acetate (3b).—A solution of 80 mg of **3a** in 3 ml of dry pyridine–acetic anhydride (2:1) was held overnight at room temperature. The solution was poured into ice water, and the mixture was extracted several times with chloroform. The chloroform solution was evaporated under vacuum and the residue was crystallized from methanol, yielding 76 mg of **3b**, mp 94.2–96.3°; $[\alpha]_D$ −40° (*c* 0.936); $\tilde{\nu}_{max}^{KBr}$ 1770, 1720, 1630, 1250, 1190, 1040 cm^{-1}; R_C 1.52 (brown-red). A characteristic decomposition pattern was obtained on gas chromatography of **3b**.

Anal. Calcd for $C_{31}H_{50}O_5$ (502.73): C, 74.06; H, 10.03. Found: C, 74.11; H, 10.29.

Proton spectra of **3b** included signals at (δ in ppm) 0.70 (3 H, C_{18} protons), 0.93 (d, J = 5 Hz, 3 H, C_{21} protons), 1.05 (3 H, C_{19} protons), 1.28 (6 H, C_{26} and C_{27} protons), 2.05 (3 H, 3β-acetoxyl protons), 2.08 (3 H, 25-peracetoxyl protons), 4.63 (m, $W_{1/2}$ = 25 Hz, 1 H, 3α proton), 5.36 (d, J = 4 Hz, 1 H, C_6-vinyl proton). For comparison cholest-5-ene-3β,25-diol 3β,25-diacetate (**4b**): 0.69 (3 H, C_{18} protons), 0.95 (d, J = 5 Hz, 3 H, C_{21} protons), 1.02 (3 H, C_{19} protons), 1.43 (6 H, C_{26} and C_{27} protons), 1.95 (3 H, 25-acetoxyl protons), 2.02 (3 H, 3β-acetoxyl protons), 4.63 (m, $W_{1/2}$ = 25 Hz, 1 H, 3α proton), 5.35 (d, J = 4 Hz, 1 H, C_6-vinyl proton); and cholesterol acetate: 0.70 (3 H, C_{18} protons), 0.87 (d, J = 7 Hz, 6 H, C_{26} and C_{27} protons), 0.91 (d, J = 6 Hz, C_{21} protons), 1.04 (3 H, C_{19} protons), 2.03 (3 H, 3β-acetoxyl protons), 4.60 (m, $W_{1/2}$ = 25 Hz, 1 H, 3α proton), 5.38 (d, J = 4 Hz, 1 H, C_6-vinyl proton).

3β-Hydroxycholest-5-ene 20α-Hydroperoxide (5a).—The mother liquor containing **5a**, X_1, X_2, and X_3 after isolation of **3a** was chromatographed on silica gel and then on Sephadex LH-20 using neat methylene chloride. From the appropriate fractions **5a** was recovered by crystallization (80 mg), and rechromatography of the mother liquor afforded 40 mg of **5a** (120 mg/kg of air-aged cholesterol), mp 146.0–149.5°; $[\alpha]_D$ −66° (*c* 0.714); $\tilde{\nu}_{max}^{KBr}$ 3400, 1630, 1050 cm^{-1}; $\tilde{\nu}_{max}^{CCl_4}$ 3620, 3560 cm^{-1}; R_C 0.93 (gray-brown).

Anal. Calcd for $C_{27}H_{46}O_3$ (418.63): C, 77.46; H, 11.07. Found: C, 77.67; H, 10.99.

3β-Acetoxychclest-5-ene 20α-Hydroperoxide 20α-Acetate (5b).—Acetylation of **5a** with acetic anhydride–pyridine in the usual fashion gave the diacetate **5b**, chromatographed on silica gel and recrystallized from methanol, 30 mg, mp 75–80°; $[\alpha]_D$ −0.3° (*c* 0.556); $\tilde{\nu}_{max}^{KBr}$ 1770, 1720, 1630, 1250, 1190, 1030 cm^{-1}; R_C 1.52 (gray-brown). A characteristic decomposition pattern was obtained on gas chromatography of **5b**.

Anal. Calcd for $C_{31}H_{50}O_5$ (502.71): C, 74.06; H, 0.03. Found: C, 73.80; H, 10.10.

Proton spectra (δ in ppm) of **5b** included 0.88 (3 H, C_{18} protons), 0.89 (d, J = 6 Hz, 6 H, C_{26} and C_{27} protons), 1.03 (3 H, C_{19} protons), 1.32 (3 H, C_{21} protons), 2.01 (3 H, 20α-peracetoxyl protons), 2.04 (3 H, 3β-acetoxyl protons), 4.60 (1 H, 3α proton), 5.38 (1 H, C_6-vinyl proton).

Unidentified Cholesterol Hydroperoxide (X_1).—After elution of the 20α-hydroperoxide **5a** from the second Sephadex LH-20 chromatographic column a small fraction containing X_1 contaminated with **3a** and **5a** was recovered. Continued elution of the column gave more **3a** (300 mg). Rechromatography of the mixed hydroperoxide fractions on Sephadex LH-20 and on silica gel, using a 0–5% linear gradient of ethyl acetate in benzene, gave fractions of X_1 free from **3a** and **5a**. After recrystallization of the hydroperoxide from benzene–ethyl acetate there was obtained 30 mg of pure X_1 free from **3a** and **5a**, mp 160–164°; $\tilde{\nu}_{max}^{KBr}$ 3400, 1630, 1050 cm^{-1}; $\tilde{\nu}_{max}^{CCl_4}$ 3620, 3560 cm^{-1}; R_C 0.95 (gray-brown); it gave a characteristic decomposition pattern on gas chromatography.

Anal. Calcd for $C_{27}H_{46}O_3$: M, 418.3446. Found: M, 418.3473.

Acetylation of 15 mg of X_1 with acetic anhydride–pyridine at room temperature overnight in the usual manner afforded a product which migrated as a single component on thin layer chromatograms (R_C 1.50) but which was resolved into two steryl acetate components on gas chromatography: X_1-a, 68%, r_T, 4.75, 2.43; X_1-b, 32%, r_T 4.28, 2.16 not worked on further.

A sample of mixed hydroperoxides enriched in X_1 was reduced at room temperature as a methanol solution with excess sodium borohydide for 15 min. The reduced product was purified by preparative thin layer chromatography, and the crude reduced product was crystallized from benzene, mp 176–179°; $\tilde{\nu}_{max}^{KBr}$ 3400, 1620, 1050, 1020 cm^{-1}; R_C 0.77 (red-brown) r_T 2.18, 1.86.

2-Methylpent-4-en-2-ol.—A ten-year old 1-kg sample of air-aged cholesterol in a 5-l. flask was subjected to vacuum for 5 days. An odorous volatile fraction (2 ml/kg) collected in a cold (−50°) trap was shown to be a mixture of low-molecular-weight components by gas chromatography on a 500 ft × 0.03 in. diameter metal capillary column coated with SF-96 silicone oil, using helium as a carrier at 15 ml/min and column temperature 20°. Selected effluent peaks were analyzed in the LKB Model 9000 mass spectrometer, the total ion current being plotted to give an elution curve. That peak recognized as 2-methylpent-4-en-2-ol also contained 2-methylpentan-2-ol, as recognized by

additional gas chromatography on Poropak Q columns (at 230°). Mass spectral analysis of the mixed alcohol fraction gave ions consistent with the structures of the two components, thus ions at m/e 85 $(M - CH_3)^+$, 59 $(C_3H_7O)^+$, 43 $(C_3H_7)^+$, and 31 $(CH_3O)^+$ associated with 2-methylpent-4-en-2-ol and ions at 87 $(M - CH_3)^+$, 69 $(C_5H_9)^+$, 59 $(C_3H_7O)^+$, 45 $(C_2H_5O)^+$, 43 $(C_3H_7)^+$, and 31 $(CH_3O)^+$ associated with 2-methylpentan-2-ol.

Mass spectra of the reference alcohols (Aldrich Chemical Co. Inc., Milwaukee, Wis.) are given for comparison (with per cents in parentheses): 2-methylpent-4-en-2-ol m/e 85 (5), 83 (3), 59 (100), 55 (8), 43 (82), 41 (42), 39 (55), 31 (35), 29 (9), 27 (24); 2-methylpentan-2-ol 87 (21), 85 (3), 69 (7), 59 (94), 45 (37), 43 (100), 41 (30), 39 (28), 31 (20), 29 (15), 27 (38).

Registry No.—Cholesterol, 57-88-5; **3a**, 23652-97-3; **3b**, 23652-98-4; **4a**, 2140-46-7; **4c**, 10525-22-1; **5a**, 23653-01-2; **5b**, 23653-02-3; **6a**, 516-72-3; **6b**, 7484-20-0; **7a**, 5255-15-2; **7b**, 23653-06-7; **8a**, 2862-58-0; **8b**, 3090-79-7; **9a**, 901-56-4; **9b**, 1913-47-9; **10a**, 145-13-1; **10b**, 1778-02-5; **11a**, 1476-64-8; **11b**, 13067-44-2; **12a**, 521-17-5; **12b**, 2099-26-5; **13a**, 53-43-0; **13b**, 853-23-6.

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A Study of Amine-Catalyzed Epimerization of 2β-Methylcholestan-3-one[1]

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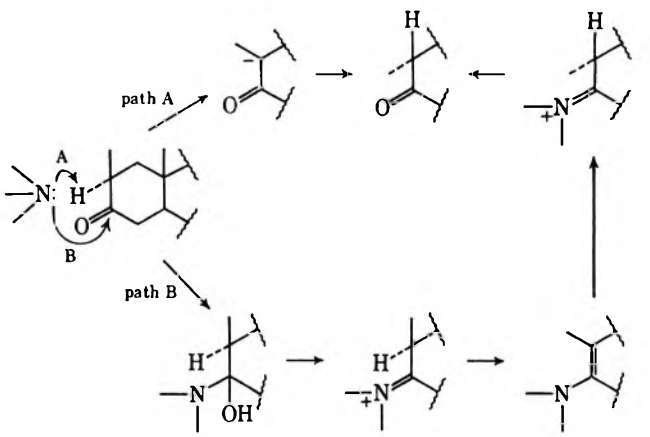
The epimerization of 2β-methylcholestan-3-one (1) to 2α-methylcholestan-3-one (2) in dioxane solution at 45° in the presence of an excess of various amines has been followed by optical rotation measurements. The results contrast with those previously found for the conversions **3** → **5** and **4** → **5**; piperidine was about as catalytically effective as pyrrolidine and hexamethylenimine, and the unhindered tertiary amine quinuclidine was only slightly less effective. These observations suggest that nucleophilic catalysis is less important in the conversion **1** → **2**, presumably because the 2β-methyl group inhibits enamine formation.

The primary question one seeks to answer in any investigation of the mechanism of an amine-catalyzed carbonyl compound reaction is whether the amine acts as a general base to remove a proton directly (as in path A below), or as a nucleophile to form an enamine which can react analogously to the enolate anion and then be reconverted to the carbonyl compound by hydrolysis (path B). Although the latter pathway was proposed many years ago,[2,3] systematic studies of this type of catalysis have appeared only within the last decade.[4-7] Most of these studies were presumably inspired by the increasing evidence of nucleophilic catalysis by amines in certain biochemical reactions.[8]

Much of this evidence comes from trapping substrate–enzyme imine intermediates by borohydride reduction.[9] However, these experiments do not prove that the imine is necessarily an intermediate and do not provide quantitative information about catalytic effectiveness. Kinetic investigations of model systems[2-7] designed to elucidate these matters by comparison of the catalytic rate constants for different amines have largely relied on relative inactivity of tertiary amines[3] and other deviations from the Brønsted catalysis law[6] as criteria for nucleophilic catalysis.



This paper describes our investigation of the epimerization of 2β-methylcholestan-3-one (1) to 2α-methylcholestan-3-one (2). This reaction was selected in order to provide a contrast to our previous study[10] of the aldol condensation–ketol dehydration sequence **3** → **4** → **5**, in which nucleophilic catalysis was inferred not only from the relative inefficiency of tertiary amines, but also from a comparison of the rates of reactions catalyzed by the three cyclic secondary amines pyrrolidine, piperidine, and hexamethylenimine. These amines are of similar base strength and steric bulk, and their kinetic basicity with respect to a given weak car-

(1) This research was presented at the Fifth Caribbean Chemical Symposium, University of the West Indies, Cave Hill, Barbados, Jan 1969.

(2) K. J. Pedersen, *J. Phys. Chem.* **38**, 559 (1934).

(3) F. H. Westheimer and H. Cohen, *J. Amer. Chem. Soc.*, **60**, 90 (1938); F. H. Westheimer, *Ann. N. Y. Acad. Sci.*, **39**, 401 (1940); F. H. Westheimer and W. A. Jones, *J. Amer. Chem. Soc.*, **63**, 3283 (1941).

(4) J. Hine, F. E. Rogers, and R. E. Notari, *ibid.*, **90**, 3279 (1968), and previous papers in this series.

(5) L. P. Koshechkina, E. A. Shilov, and A. A. Yasnikov, *Ukr. Khim. Zh.*, **35**, 55 (1969), and previous papers in this series. These extensive reports by Yasnikov and coworkers contain many arguable mechanistic suggestions. Discussion of these papers has been promised by Hine [J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Amer. Chem. Soc.*, **88**, 3367 (1966)].

(6) M. L. Bender and A. Williams, *ibid.*, **88**, 2502 (1966).

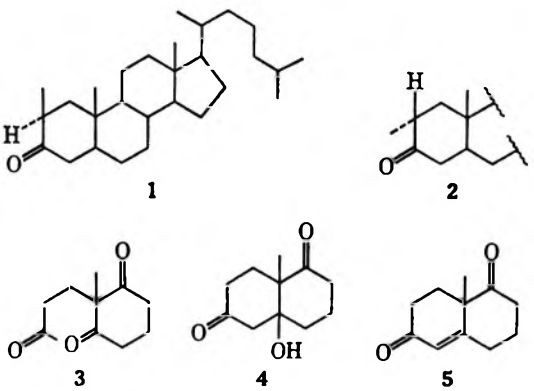
(7) G. E. Lienhard and T-C. Wang, *ibid.*, **90**, 3781 (1968).

(8) See W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 2, especially pp 116–146, for a review and specific references.

(9) For example: (a) S. Warren, B. Zerner, and F. H. Westheimer, *Biochemistry*, **5**, 817 (1966); (b) J. C. Speck, Jr., P. T. Rowley, and B. L. Horecker, *J. Amer. Chem. Soc.*, **85**, 1012 (1963), and B. L. Horecker, T. Cheng, E. Grazi, C. Y. Lai, P. Rowley, and O. Tchola, *Fed. Proc.*, **21**, 1023 (1962); (c) D. Portsmouth, A. C. Stoolmiller, and R. H. Abeles, *J. Biol. Chem.*, **242**, 2751 (1967).

(10) T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Lett.*, 3889 (1965).

bon acid (such as a ketone) should be similar. They differ, however, in the ease with which they will form enamines.[11] It is less easy to make an atom of a six-membered ring trigonal than an atom of a five- or seven-membered ring, as has been shown in several differing kinds of reactions.[12] Formation of an iminium ion en route to an enamine (as in path B) will thus be least favorable with a six-membered-ring catalyst, and piperidine would be expected to be the least effective catalyst of the three amines, as observed in our earlier studies.[10]



However, before a conclusion was reached that a minimum in rate constant for piperidine is diagnostic of nucleophilic catalysis, it was desirable to show that a reaction which would *not* be expected to be nucleophilically catalyzed did not show such a minimum. A reaction involving proton abstraction from the 2′ position of a carbonyl compound bearing a 2 substituent seemed appropriate for this study, since a sizable 2 substituent will tend to impede nucleophilic addition to the carbonyl group more than it will proton abstraction.[13]

In a study very relevant to our choice of a system, Malhotra and Johnson have presented convincing evidence that the proton in the 2′ position of 2-methylcyclohexanone was not detectably removed during treatment with pyrrolidine which effected substantial deuterium incorporation at the 6 positions.[14] Although such data are not available for other amines, and despite the fact that Gurowitz has shown[15] that amines other than pyrrolidine do not to the same degree avoid formation of 2-methyl-$\Delta^{1,2}$-enamines, use of a 2-methyl ketone as substrate should *at least* eliminate the previously observed[10] unusually effective catalysis by pyrrolidine. We therefore chose to study the epimerization of **1**, which is a relatively simple reaction involving in essence only removal of the 2α proton and reprotonation from the β side.[16]

The same seven amines were used as in the previous studies:[10] the three discussed above, plus morpholine (similar in structure, but a weaker base), *n*-butylamine (a primary amine), triethylamine (a tertiary amine), and quinuclidine (an unhindered tertiary amine). The same solvent, dioxane, was also chosen. This is convenient from the standpoint of solubility of substrate, but has the disadvantage that the relative base strengths of the amines are uncertain. It is not safe to assume that the relationships among pK_a's determined in water will hold in other solvents.[17] It would be meaningless to attempt to construct a Brønsted plot, for example, unless the base strengths of the amines in dioxane were determined. However, the similarity in structure of many of the amines used in this study probably minimizes differences among them in the dependence of base strength upon medium.

The required substrate, 2β-methylcholestan-3-one (**1**), can be readily prepared in large quantity by a synthetic sequence developed by Nickon and DiGiorgio.[18] The epimerization of **1** to **2** was followed by measurement of the accompanying change in optical rotation. Solutions of **1** in dioxane were indefinitely stable without added amine. Relatively large concentrations of amine were necessary to effect the conversion of **1** to **2** at conveniently measurable rates, even at 45°. In the presence of amines the optical rotation of solutions of **1**, measured at 365 mμ (where the difference in rotation between **1** and **2** is much larger than at 589 mμ), decreased until it corresponded to a mixture of *ca.* 90% **2** and 10% **1**, in those cases where the reaction was followed that far. Evaporation of such a product mixture (from a pyrrolidine-catalyzed epimerization) afforded 89% crude and 22% pure **2**.

Good pseudo-first-order kinetic plots were obtained using the observed final rotation or the value calculated for 90% epimerization in reactions which were too slow to be followed to completion. A typical plot is shown in Figure 1. It was not determined whether the approximately 9:1 mixture of **2** and **1** represented an equilibrium mixture.[19] If this were the case, the rate constants discussed below are the sum of the rate for $1 \rightarrow 2$ and the smaller rate for $2 \rightarrow 1$.[20] In view of the uncertainties involved and the relatively small potential correction for the rate of $2 \rightarrow 1$, no adjustment of

(11) Quantitative comparisons of the facility of various amines for enamine formation are lacking, but the assertion that pyrrolidine, piperidine, and hexamethylenimine differ is substantiated by the discussion and experimental procedures given by (a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963); (b) A. A. Brizzolara, Jr., Ph.D. Dissertation, Columbia University, 1960.

(12) H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957); H. C. Brown, *J. Chem. Soc.*, 1248 (1956); H. C. Brown, J. H. Brewster, and H. Schecter, *J. Amer. Chem. Soc.*, **76**, 467 (1954). These ideas were first applied to enamine formation by G. Stork, *et al.*[11a]

(13) (a) W. P. Jencks, ref 8, p 96; (b) also, it can be inferred from experimental procedures given in ref 11a and 11b that the overall rate of enamine formation from 2-methylcyciohexanone is slower than from cyclohexanone.

(14) S. K. Malhotra and F. Johnson, *Tetrahedron Lett.*, 4027 (1965).

(15) W. D. Gurowitz and M. A. Joseph, *ibid.*, 4433 (1965).

(16) It is assumed in this study that all amines have approximately the same *ratio* for α *vs.* β deprotonation or reprotonation of a given species. In this connection it should also be noted that **1** probably has ring A predominantly in the twist conformation [K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961)], which is favorable for removal of the 2α proton *via* the stereoelectronically favored pathway [see ref 14 and F. Johnson, *Chem. Rev.*, **68**, 375 (1968), for pertinent discussions of the subtleties of a very closely analogous situation].

(17) See F. M. Menger and J. H. Smith, *J. Amer. Chem. Soc.*, **91**, 5346 (1969), for consideration of the importance of the effect of solvent on base strength in kinetic studies.

(18) J. DiGiorgio, Ph.D. Dissertation, Johns Hopkins University, 1960.

(19) A. Nickon and J. DiGiorgio (ref 18) have determined that the equilibrium composition of these epimers in chloroform containing hydrogen chloride at room temperature is *ca.* 96% **2** and 4% **1**. Thus a 9:1 mixture is not unreasonable for the equilibrium composition in dioxane containing amines at 45°. However, experimental determination of the equilibrium composition of **1** and **2** under these conditions might not be straightforward owing to the presence at equilibrium of some enamine or carbinolamine species of different rotation.

(20) For discussions of the kinetics of first-order reversible reactions, and derivation of the expression $k_{obsd} = k_{forward} + k_{reverse}$, see W. P. Jencks, ref 8, p 586; A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, 2nd ed, New York, N. Y., 1961, p 185.

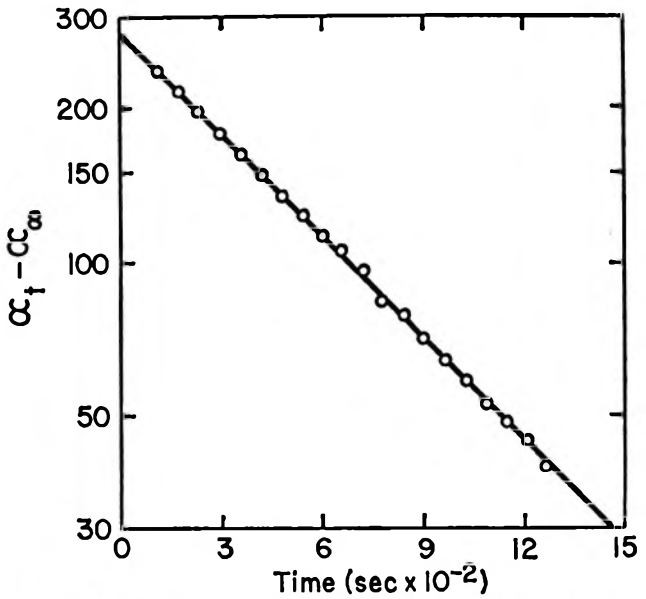


Figure 1.—Semilogarithmic plot of the change in optical rotation at 365 mμ of a solution of 2β-methylcholestan-3-one (1) (2.3×10^{-2} *M*) in dioxane containing pyrrolidine (5.7 *M*) at 45°.

the observed rates has been made in the following discussion.

In Table I are shown the specific second-order rate constants (k_2) obtained by dividing k_{obsd} by the appropriate amine concentration. In the case of pyrrolidine the concentration of amine was varied 60-fold from 0.1 to 6.0 *M*. Over this concentration range k_2 for pyrrolidine increased about threefold. Although from our data we cannot exclude a small incursion of a catalytic term greater than first order in amine, it seems reasonable that this increase is due instead to the changing nature of the medium, which contains *ca.* 1% amine at 0.1 *M*, as opposed to *ca.* 50% amine at 6 *M*.

TABLE I

EFFECTIVENESS OF AMINES IN CATALYZING THE EPIMERIZATION OF 1 TO 2 IN DIOXANE SOLUTION AT 45°

Amine	Structure	pK_a[a]	Amine concn, *M*	$k_2 \times 10^6$ (M^{-1} sec^{-1})
Pyrrolidine	$(CH_2)_4NH$	11.32	5.7	25
Piperidine	$(CH_2)_5NH$	11.20	6.6	10
Hexamethylenimine	$(CH_2)_6NH$	11.10	5.3	4.4
n-Butylamine	$CH_3CH_2CH_2CH_2NH$	10.61	7.2	11
Morpholine	$O(CH_2CH_2)_2NH$	8.36	6.2	0.44
Quinuclidine	$HC(CH_2CH_2)_3N$	10.95	0.25	1.0
Triethylamine	$(CH_3CH_2)_3N$	10.75	3.5	0.01

[a] The pK_a's are literature values for aqueous solution at 25°.

Accordingly, it is important to compare rate constants obtained at approximately the same concentration of catalyst. This is done in Table I with the exception of quinuclidine, which was run only at a much lower amine concentration. The value of k_2 for quinuclidine thus is almost certainly somewhat lower than it should be for comparison with the other rate constants.

In Table II these relative rates are compared with those previously reported for the conversions **3** → **5** and **4** → **5**.[10] Clearly different trends appear. There is less difference among the amines in the epimerization of

TABLE II

COMPARISON OF AMINE CATALYSIS OF CONVERSIONS 1 → 2, 3 → 5, AND 4 → 5

Amine	1 → 2, k_{rel}	3 → 5,[a] k_{rel}	4 → 5,[a] k_{rel}
Pyrrolidine	2.5	120	1000
Piperidine	1.0	1	1
Hexamethylenimine	0.44	5	15
n-Butylamine	1.1	50	50
Morpholine	0.044	0.4	1
Quinuclidine	0.1	0.03	0.02
Triethylamine	0.001	0.005	0.02

[a] See ref 2.

1. Quinuclidine, the unhindered tertiary amine, does not differ markedly from the secondary and primary amines in catalytic effectiveness. The low epimerization rate with triethylamine can be ascribed to steric hindrance to proton abstraction.[21] Most significantly for our purposes, there is no minimum in the rate of epimerization of 1 with piperidine, compared with pyrrolidine and hexamethylenimine. The rate constants for these three homologs simply decrease slightly as the ring becomes larger.

These contrasts between amine catalysis of 1 → 2 and the earlier results[10] can be explained, as discussed above, on the basis of steric hindrance to the formation of the appropriate enamine from 1, making nucleophilic catalysis less important relative to direct proton abstraction. These results lend validity to the use of a comparison of catalytic effectiveness *vs.* amine ring size as a criterion for nucleophilic catalysis. Further studies of amine catalysis, using this and other criteria, are in progress.[22]

Experimental Section[23]

2β-Methylcholestan-3-one (1).—The preparation of 2β-methylcholestan-3-one (1) was carried out by the procedures described by DiGiorgio.[18] Cholestan-3-one was converted to 2-hydroxymethylenecholestan-3-one, which was reduced with lithium aluminum hydride to 2-methylenecholestan-3β-ol (48%). Rearrangement of 2-methylenecholestan-3β-ol in ethyl acetate solution in the presence of palladium on carbon in a hydrogen atmosphere afforded 96% 2β-methylcholestan-3-one (1), mp 83–86°. When the reaction was run without hydrogen the rearrangement did not take place. Recrystallization of 1 from ether–methanol raised this to mp 99.5–100° (lit.[18] mp 98–99°; lit.[24] mp 96–97°): ir (KBr) 5.83 μ; $[\alpha]_{365}^{dioxane,\ 45}$ +470°; $[\alpha]_{578}^{dioxane,\ 45}$ +118°; (lit.[18] $[\alpha]_{589}^{CHCl_3,25}$ +122°; lit.[24] $[\alpha]_{589}^{CHCl_3,\ 25}$ +86°).

2α-Methylcholestan-3-one (2).—Preparation of 2 was accomplished by epimerization of 1, both with sulfuric acid and with pyrrolidine as catalyst. A solution of 0.566 g (1.4×10^{-3} mol) of 1 in a mixture of 45 ml of 95% ethanol and 1.5 ml of 20% aqueous sulfuric acid was refluxed for 4 hr. The mixture was partitioned between ether and water, and the ether layer was dried and evaporated to afford 0.426 g of 2, mp 108–112°. Repeated recrystallization from methanol raised this to mp 116.5–117° (lit.[18] mp 119.5–120.5°; lit.[24] mp 119–120°): ir

(21) For a general discussion of steric hindrance to general base catalysis and references, see (a) F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 1773 (1963). For examples of relative ineffectiveness of triethylamine in reactions involving abstraction of a weakly acidic proton, see (a) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *ibid.*, **87**, 5050 (1965); (b) L. R. Fedor, *ibid.*, **89**, 4479 (1967); (c) J. Weinstock, R. G. Pearson, and F. G. Bordwell, *ibid.*, **78**, 3473 (1956).

(22) See, *e.g.*, G. T. Sinner and T. A. Spencer, Abstract P-116, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(23) Melting points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer. Specific rotations listed for pure substances are the average value from two separate determinations.

(24) Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 5220 (1949).

(KBr) 5.84 μ; $[\alpha]_{365}^{\text{dioxane, 45}}$ +118°; $[\alpha]_{578}^{\text{dioxane, 46}}$ +28° (lit.[18] $[\alpha]_{589}^{\text{CHCl}_3, 25}$ +36°; lit.[24] $[\alpha]_{589}^{\text{CHCl}_3, 25}$ +32°). This material showed one spot upon tlc on silica gel using 3:2 ether–benzene.

Preparative epimerization of **2** was also accomplished by allowing a mixture of 0.083 g (2.1×10^{-4} mol) of **1**, 3.62 g (0.051 mol) of pyrrolidine, and 6.2 ml of dioxane to stand at 45°. After 60 min (*ca.* $8 \times t_{1/2}$), the optical rotation corresponded to a mixture of 89% **2** and 11% **1**. No further change in rotation was observed for 54 hr. The mixture was evaporated to dryness *in vacuo*, affording 0.077 g (89%) of yellowish solid, mp 92–103°. Three recrystallizations from methanol afforded 0.019 g (22%) of **2**, mp 115–116.5°, which had an ir spectrum identical with that of the material prepared by acid-catalyzed epimerization.

Other Materials.—All amines except quinuclidine were purchased from the Aldrich Chemical Company and were redistilled twice from barium oxide, the last time directly before use. Purity of each amine was checked by vpc once, but not routinely. Quinuclidine was prepared by reduction of 3-quinuclidone (derived from Aldrich 3-quinuclidone hydrochloride) by the Huang-Minlon procedure,[25] with a careful work-up to avoid evaporation of the product, and was purified by sublimation at aspirator pressure at 70°. The sublimed material had mp 155–158° (sealed tube) (lit.[26] mp 158°). Matheson Coleman and Bell spectroquality reagent dioxane was used as supplied from freshly opened bottles.

Kinetic Measurements.—The conversion **1** → **2** was monitored by following the change in optical rotation of solution of **1** in dioxane on a Perkin-Elmer Model 141 automatic digital readout polarimeter. Temperature was controlled by a Haake water circulating thermostating unit at 45.0°. The polarimeter cell used was 1 decimeter in length with a volume of 0.85 ml. Polarized light of 365-mμ wavelength was chosen because the difference between the rotations of **1** and **2** is greater at this wavelength than at the other, longer wavelengths available with the polarimeter.

Solutions of **1** in dioxane at 45° showed no change in rotation on standing for several hours. In many cases, mixing of amine with the dioxane solution of **1** was done at room temperature and not on materials preheated to 45°, but the mixtures were quickly inserted into the thermostated polarimeter. Good pseudo-first-order kinetic plots were obtained in all cases, for over 80% reaction in some cases. Many of the reactions were too slow to be followed conveniently to completion, and kinetic data were obtained for as little as 20% conversion.

The linear pseudo-first-order plots of log ($\alpha_t - \alpha_\infty$) (specific rotation at time t minus specific rotation at the completion of reaction) *vs.* time were used to determine $t_{1/2}$ for the reactions, and k_2, the specific second-order rate constants (in $\text{sec}^{-1}\ M^{-1}$) were calculated by use of the expression $k_2 = k_{obsd}/[\text{amine}] = 0.693/[t_{1/2}][\text{amine}]$. In those cases where α_∞ was not observed experimentally, it was calculated using the assumption that α_∞ would correspond to 90% conversion of **1** to **2**. This method gave linear pseudo-first-order plots. As noted in the discussion, if the α_∞ at 90% conversion corresponds to the equilibrium composition of **1** and **2** under the prevailing conditions, then the k_2's derived are equal to the sum of the forward and reverse reaction rate constants.[20]

All amines except quinuclidine and triethylamine were run at several concentrations, and gave somewhat larger rate constants at higher amine concentrations as the proportion of amine in the mixture increased.

Acknowledgment.—The authors are indebted to Professor Alex Nickon for providing details of the preparation of **1**. Considerable earlier experimentation by Mr. H. A. Budd, Jr., and Mr. E. J. L. Wasserman on the epimerization of 2β-acetoxycholestan-3-one served both to demonstrate the need for a better substrate and to familiarize us with the techniques used in the optical rotation kinetics study. We are particularly grateful to Professor K. L. Williamson and his colleagues at Mount Holyoke College, who graciously allowed us unlimited access to their polarimeter and afforded patient guidance in its use. Financial support was provided by PHS Research Grant AM11815, from the National Institute of Arthritis and Metabolic Diseases.

Registry No.—**1**, 14528-10-0; **2**, 2097-78-1.

(25) Huang-Minlon, *J. Amer. Chem. Soc.*, **71**, 3301 (1949).
(26) J. Meisenheimer, *Justus Liebigs Ann. Chem.*, **420**, 190 (1920).

The Chemical Synthesis of the 1,2,4-Triazole Nucleosides Related to Uridine, 2′-Deoxyuridine, Thymidine, and Cytidine[1]

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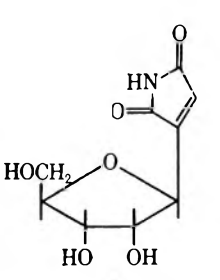
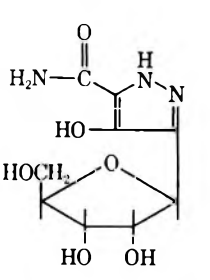
The synthesis of 1-(β-D-ribofuranosyl)urazole (**3**), 1-(2-deoxy-β-D-ribofuranosyl)urazole (**14**), and 1-(2-deoxy-β-D-ribofuranosyl)-2-methylurazole (**13**) has been accomplished *via* the trimethylsilyl derivatives of urazole and 1-methylurazole. The synthesis of the corresponding nucleoside related to cytidine, 3-amino-1-(β-D-ribofuranosyl)-1,2,4-triazolin-5-one (**26**), was accomplished in a lengthy procedure involving 3-bromo-5-nitro-1,2,4-triazole in the fusion process. Evidence in support of the site of glycosylation has been presented. The reaction mechanism involved in the various glycosylation procedures of the 1,2,4-triazole ring has been discussed.

The nucleoside antibiotic showdomycin, isolated from cultures of *Streptomyces showdoensis*,[3] has been shown by these laboratories[4] to possess structure **1**. Another antibiotic, pyrazomycin, has been shown[5] to possess the nucleoside structure **2**. It is thus quite clear that nucleoside derivatives of five-membered heterocyclic rings



1



2

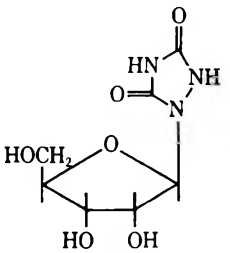
(1) Supported in part by a NASA Traineeship to J. T. Witkowski.
(2) ICN Nucleic Acid Research Institute, 2727 Campus Drive, Irvine, Calif. 92664.
(3) H. Nishimura, M. Mayama, Y. Komatsu, H. Kato, N. Shimaoka, and Y. Tanaka, *J. Antibiot.*, **17A**, 148 (1964).
(4) K. R. Darnall, L. B. Townsend, and R. K. Robins, *Proc. Nat. Acad. Sci. U. S.*, **57**, 548 (1967).
(5) R. H. Williams, K. Gerzon, M. Hoehn, M. Gorman, and D. C. DeLong, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, No. MICR 38.

are of considerable interest as compounds of potent biological activity. The only known synthetic derivatives of this type described in the chemical literature are nucleoside derivatives of imidazoles.[6-8]

The biological activity of the antibiotic 5-azacytidine has been reviewed[9] and a new synthesis was recently reported from our laboratories.[10] Thus the insertion of an additional nitrogen atom into the pyrimidine ring in place of C_5 in the case of cytidine does indeed result in a compound with unusual biological properties.

In the present studies an –NH– has been substituted for C_5 and C_6 of the naturally occurring pyrimidine nucleosides. The fact that the five-membered ring in showdomycin results in an antibiotic which specifically inhibits uridine monophosphate kinase and uridine phosphorylase[11] is strong suggestion that these 1,2,4-triazole nucleoside analogs will resemble the natural pyrimidine nucleosides in various biochemical systems.

Another feature of compounds such as 1-(β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (**3**) is the fact that **3** also strongly resembles pseudouridine. Compound **3** exhibits two –NH– functions in structural similarity to pseudouridine. Pseudouridine is of current



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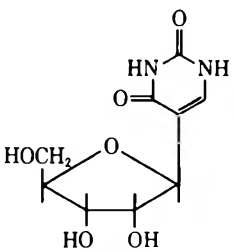
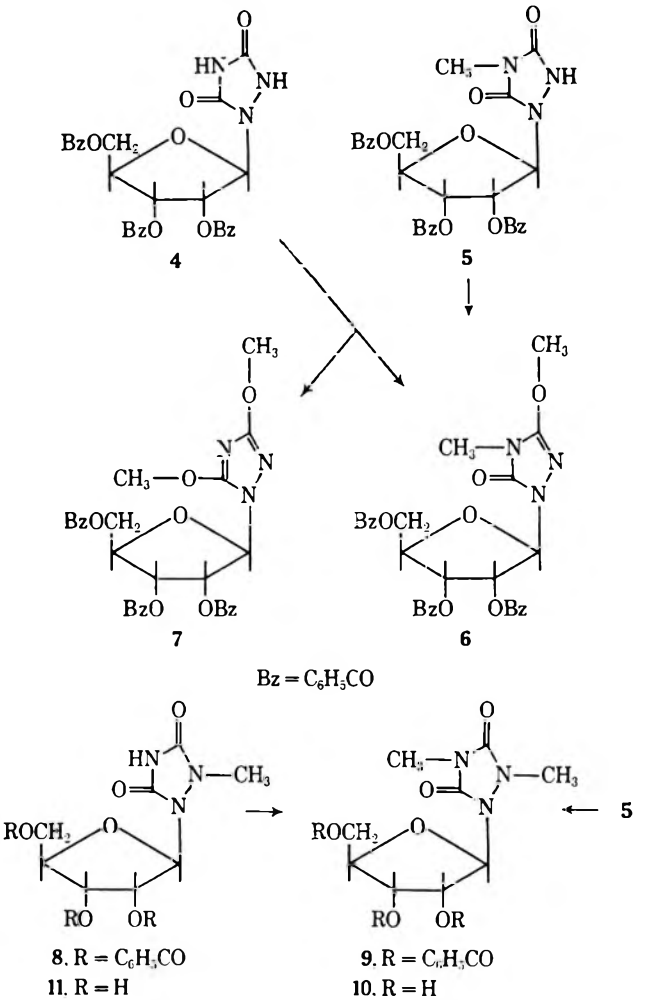


pseudouridine

interest as a minor component of various *t*-RNA's and has recently been isolated as a major product from the culture filtrates of *Streptoverticillium ladakanus*.[12]

The first goal of the presently described work was the chemical synthesis of 1-(β-D-ribofuranosyl)urazole (**3**). The trimethylsilyl derivative of urazole was prepared from urazole and hexamethyldisilazane according to the general method of Wittenburg.[13] Treatment of the trimethylsilyl derivative of urazole with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile at room temperature provided a single nucleoside, product **4**, in 84% yield. Elemental analysis of **4** was consistent with the structure 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)urazole (**4**). It was possible that **4** was an N-4 ribosyl derivative or an *O*-glycoside. The assignment of the site of glycosylation in the 1,2,4-triazole ring proved to be rather difficult. Since this ring system does not exhibit an absorption maximum in the uv spectrum above 214 mμ, the typically classical procedures could not be used. The actual structure **4** was established by methylation of the blocked nucleoside **4** with diazomethane and by further comparison of the methylated product **6** with **6** prepared by an unambiguous route. For this purpose 4-methylurazole,[14] which could form only a single *N*-nucleoside, was silylated and the trimethylsilyl derivative was treated with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile (Scheme I). The product obtained gave correct ele-

SCHEME I



mental analysis and pmr spectrum for 4-methyl-1-(2,3,-5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (**5**). Methylation of **5** with diazomethane provided an *O*-methyl derivative **6** as shown by elemental analysis and the pmr signal at δ 3.81, which is indicative of an *O*-methyl rather than an N-methyl group. The assignment of the signal at δ 3.81 to an *O*-methyl group is supported by comparison of the pmr spectrum of **6** with the spectra of **5** and **8**, which exhibit signals for the N-4 and N-2 methyl groups at δ 3.03 and 3.18, respectively. Since the structure of the 4-methylurazole derivative **5** was established by synthesis, the product from the methylation of **5** was 3-methoxy-4-methyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-1,2,4-triazolin-5-one (**6**), which was shown to be identical with the major product from the methylation of the urazole nucleoside **4** by rigorous comparison of ir and pmr spectra and mixture melting point. A small amount of a second product **7** was isolated by column chromatography from the methylation of **4**. The pmr spectrum, which showed signals for two *O*-methyl groups at δ 3.84

(6) R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, **90**, 2661 (1968).

(7) R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 311 (1967).

(8) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **33**, 3593 (1968).

(9) L. J. Hanka, J. S. Evans, D. J. Mason, and A. Dietz, *Antimicrob. Ag. Chemother.*, 619 (1966).

(10) M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **35**, 491 (1970).

(11) S. Roy-Burman, P. Roy-Burman, and D. W. Visser, *Cancer Res.*, **28**, 1605 (1968).

(12) R. J. Suhadolnik, private communication.

(13) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).

(14) J. C. Stickler and W. H. Pirkle, *J. Org. Chem.*, **31**, 3444 (1966).

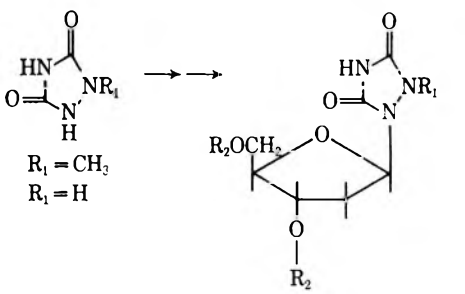
and 4.06, established this compound as 3,5-dimethoxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (**7**). Formation of this dimethoxy derivative conclusively demonstrated that the product **4** from the glycosylation of the trimethylsilyl derivative of urazole is not an *O*-glycoside.

The pmr spectrum of the methylated product, 3-methoxy-4-methyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-trizolin-5-one (**6**), exhibited a signal for the anomeric proton at δ 6.25 with a coupling constant of less than 1 Hz, which established[15] the β configuration for 1-(β-D-ribofuranosyl)urazole (**3**). Debenzoylation of **4** with methanolic ammonia provided 1-(β-D-ribofuranosyl-1,2,4-triazolidine-3,5-dione (**3**), 1-(β-D-ribofuranosyl)urazole, a structural analog of uridine.

The trimethylsilyl derivative of 1-methylurazole[16] on treatment with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile at room temperature provided a crystalline-blocked nucleoside in 77% yield. Elemental analysis and the pmr spectrum of the product were consistent with the structure 2-methyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)urazole (**8**), but, as in the case of urazole, glycosylation at either N-1 or N-4 is possible. Methylation of **8** with methyl iodide and potassium carbonate in dimethylformamide provided **9** with two nonequivalent *N*-methyl groups as shown by the pmr spectrum. Debenzoylation of **9** with sodium methoxide in methanol afforded a crystalline compound 2,4-dimethyl-1-(β-D-ribofuranosyl)urazole (**10**). The structure of **10** was established by rigorous comparison with the same product (**10**) obtained by similar methylation of 4-methyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (**5**) followed by debenzoylation with sodium methoxide in methanol. Signals for two N-methyl groups were observed in the pmr spectrum of **10** at δ 3.03 and 3.23. The nucleoside obtained by glycosylation of the trimethylsilyl derivative of 1-methylurazole is thus established as 2-methyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (**8**). Debenzoylation of **8** with methanolic ammonia provided 2-methyl-1-(β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (**11**).

The thymidine analog **13** was obtained by fusion of the trimethylsilyl derivative of 1-methylurazole with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride[17] *in vacuo* at 110°. A crystalline product was obtained in 41% yield which had an elemental analysis in agreement with that required for 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl)-2-methylurazole (**12**). The blocking groups were removed from **12** with methanolic ammonia to afford a crystalline product 1-(2-deoxy-β-D-ribofuranosyl)-2-methylurazole (**13**). The pmr spectrum of **13** exhibited a pseudotriplet centered at δ 5.87 (D_2O) (one proton) with a peak width of 14.2 Hz and an apparent splitting constant of 7.1 Hz. This is in agreement with the values reported[18] for the anomeric protons of several 2′-deoxy-β-D-ribofuranosyl nucleosides (peak width of 13.0 ± 1 Hz and an apparent splitting constant of 6.5 ± 0.5 Hz) but not in agreement with the values[18] for the anomeric proton of 2′-deoxy-α-D-ribofuranosyl nucleosides (a quartet with $J_{H_{1'}}$ of 3.1 ± 0.4 Hz and 7.2 ± 0.3 Hz with a peak width of 10.4 ± 0.4 Hz). On this basis the anomeric configuration of **13** was assigned as β. The 2′-deoxyuridine analog **14** was similarly prepared from a mixture of the trimethylsilyl derivative of urazole and 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride, which was heated *in vacuo* at 110° to give a 67% yield of the blocked nucleoside. Treatment with methanolic ammonia provided 1-(2-deoxy-β-D-ribofuranosyl)urazole or 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,2,4-triazolidine-3,5-dione (**14**). The pmr spectrum of **14** exhibited a poorly resolved multiplet with a peak width of 14 Hz for the anomeric proton. This peak width is consistent with the β configuration[18] for **14** and this assignment, as well as the site of glycosylation of **14**, was further confirmed by methylation of the *p*-toluoyl derivatives of **13** and **14** with methyl iodide and potassium carbonate in dimethylformamide, which in each case provided the same product, 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-2,4-dimethyl-1,2,4-triazolidine-3,5-dione.

Attempts to extend the silylation and alkylation procedure to the cytosine analog, 3-amino-1,2,4-triazolin-5-one,[19] were unsuccessful. Reaction of the trimethylsilyl derivative of 3-amino-1,2,4-triazolin-5-one with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide resulted in formation of intractable products. These results appeared to be largely due to dehydrohalogenation of the blocked bromo sugar. This type of elimination reaction is often observed with nitrogen heterocycles which possess basic substituents.



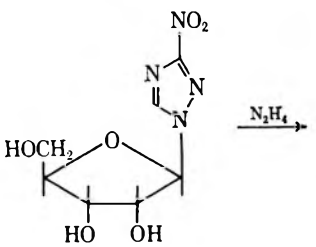
12, R_2 = *p*-$CH_3C_6H_4CO$, $R_1 = CH_3$
13, $R_2 = H$, $R_1 = CH_3$
14, $R_2 = H$, $R_1 = H$

In an effort to study other procedures for glycosylation of the 1,2,4-triazole ring, the parent compound, 1,2,4-triazole, was employed. The trimethylsilyl derivative of 1,2,4-triazole treated in acetonitrile with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide gave, after column chromatography, a 54% yield of blocked nucleoside. Deblocking with sodium methoxide gave a 90% yield of 1-(β-D-ribofuranosyl)-1,2,4-triazole (**15**). The structure of **15** was readily apparent since two singlets were observed in the pmr spectrum (δ 8.06 and 8.80). This was proof of the site of glycosylation since the pmr spectrum of the isomeric 4-(β-D-ribofuranosyl)-1,2,4-triazole[20] exhibits a singlet for the C_3 and C_5 protons due to symmetry.

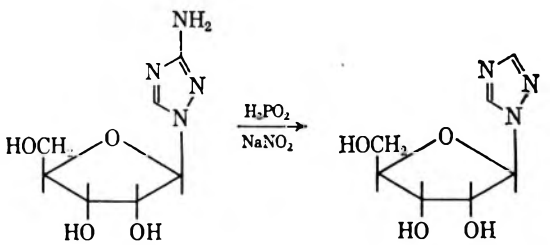
(15) R. U. Lemieux and D. R. Lineback, *Annu. Rev. Biochem.*, **32**, 155 (1963).
(16) F. Arndt, L. Loewe, and A. Tarlan-Akon, *Rev. Fac. Sci. Univ. Istanbul*, **13A**, 127 (1948); *Chem. Abstr.*, **42**, 8190 (1948).
(17) M. Hoffer, *Chem. Ber.*, **93**, 2777 (1960).
(18) M. J. Robins and R. K. Robins, *J. Amer. Chem. Soc.*, **87**, 4934 (1965).
(19) G. I. Chipen, R. P. Bokalder, and V. Ya. Grinshtein, *Chem. Heterocycl. Compounds (USSR)*, **2**, 79 (1966).
(20) J. T. Witkowski and R. K. Robins, to be published.

3-Nitro-1,2,4-triazole[21,22] was prepared for the present study by oxidation of 3-amino-1,2,4-triazole with pertrifluoroacetic acid.[23] 3-Nitro-1,2,4-triazole (**16**) is of interest in its own right since it may be considered an aza derivative of the antibiotic azomycin[24,25] (2-nitroimidazole). In view of the success of the fusion reaction with 2-nitroimidazole to yield 1-(β-D-ribofuranosyl)-2-nitroimidazole[7] the direct fusion of 3-nitro-1,2,4-triazole (**16**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose was investigated. At 190° for 30 min in the absence of catalyst, an 88% yield of crystalline 3-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (**17**) was obtained. The β configuration of **17** was assigned on the basis of the coupling constant of the anomeric proton ($J_{1',2'}$ = 1.2 Hz).[15] Assignment of the site of glycosylation was next studied.

When **17** was debenzoylated with sodium methoxide in methanol and the resulting 3-nitro-1-(β-D-ribofuranosyl)-1,2,4-triazole (**18**) reduced with hydrazine,[26] an



18



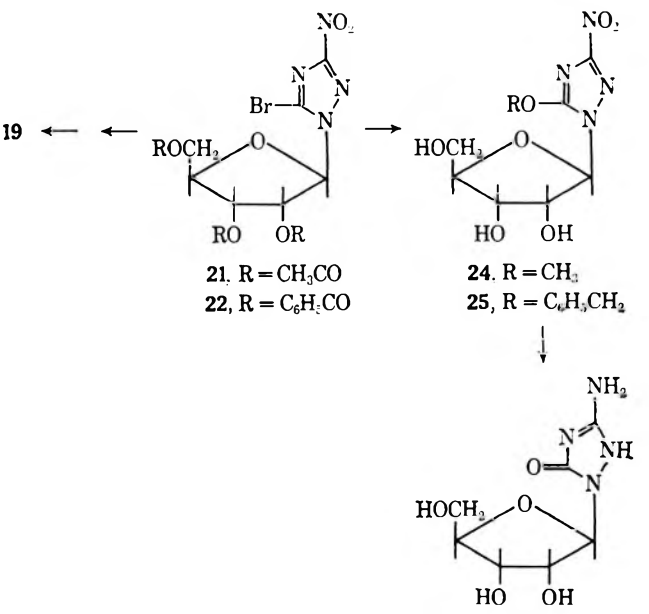
19 **15**

88% yield of 3-amino-1-(β-D-ribofuranosyl)-1,2,4-triazole (**19**) was obtained. Reductive deamination of **19** with nitrous acid in the presence of hypophosphorous acid afforded 1-(β-D-ribofuranosyl)-1,2,4-triazole (**15**).

Since the deaminated product **15** was a 1-substituted 1,2,4-triazole, the 3-amino-1,2,4-triazole nucleoside (**19**) could not be substituted at position 4. However, deamination of either 3-amino-1-(β-D-ribofuranosyl)-1,2,4-triazole or 5-amino-1-(β-D-ribofuranosyl)-1,2,4-triazole would provide 1-(β-D-ribofuranosyl)-1,2,4-triazole (**15**), since the 3 and 5 positions are equivalent in the unsubstituted 1,2,4-triazole. To distinguish between these two possible structures, the deamination of **19** was repeated in D_2O with hypophosphorous acid which had been equilibrated with D_2O.[27] This procedure is a modification of a method reported for introducing deuterium into aromatic compounds.[28] The pmr spectrum of the product obtained from deamination was identical with the spectrum of 1-(β-D-ribofuranosyl)-1,2,4-triazole (**15**) except that the intensity of the signal for the aromatic proton (3-H) at δ 8.06 (DMSO-d_6) was reduced by 73%. Exchange of the ring protons with D_2O had not occurred as shown by control experiments in which only slight exchange of the proton in the 5 position was noted after a prolonged time.

These results demonstrated that the amino group had occupied the 3 position and support the structure of **19** as 3-amino-1-(β-D-ribofuranosyl)-1,2,4-triazole. The nucleoside obtained by fusion of 3-nitro-1,2,4-triazole is therefore 3-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (**17**). The structure **19** is based on the assignment of the downfield proton in **15** at δ 8.80 as H_5, adjacent to the site of glycosylation. The electronegative effect of the sugar causes the expected deshielding of the adjacent proton approximately 0.6 ppm over that of H_5 as determined in 1-methyl-1,2,4-triazole.[29]

Bromination of 3-nitro-1,2,4-triazole in the presence of sodium hydroxide gave 3-bromo-5-nitro-1,2,4-triazole (**20**). The fusion of **20** with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose proved highly successful to afford 93% yield of a single crystalline product **21**. Use of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the fusion procedure with **20** provided **22**. The site of glycosylation was established when **22** was subjected to catalytic hydrogenation with palladium on carbon. Reduction of the nitro group and simultaneous debromination occurred to yield 3-amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (**23**). Debenzoylation of **23** with sodium methoxide in methanol afforded 3-amino-1-(β-D-ribofuranosyl)-1,2,4-triazole (**19**) identical in all respects with **19** previously pre-



21, R = CH_3CO
22, R = C_6H_5CO
24. R = CH_3
25, R = $C_6H_5CH_2$

26

pared *via* reduction of **18**. The structure of the nucleoside obtained by fusion of 3-bromo-5-nitro-1,2,4-tri-

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azole is thus assigned as 5-bromo-3-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole (**21**).

When deacetylation of **21** was attempted with sodium methoxide in methanol at room temperature, the bromo group was rapidly displaced. The product obtained in 69% yield was 5-methoxy-3-nitro-1-(β-D-ribofuranosyl)-1,2,4-triazole (**24**).

In order to obtain an oxo substituent in the 5 position of the 1,2,4-triazole nucleoside (**26**), displacement of the 5-bromo group of **21** with concomitant deacetylation was effected with sodium benzyloxide in benzyl alcohol at room temperature. After column chromatography of the crude reaction mixture to remove benzyl acetate and excess benzyl alcohol, a 40% yield of 5-benzyloxy-3-nitro-1-(β-D-ribofuranosyl)-1,2,4-triazole (**25**) was obtained. Catalytic reduction of the nitro group and simultaneous hydrogenolysis of the benzyl ether with palladium on carbon in the presence of hydrogen afforded the cytidine analog, 3-amino-1-(β-D-ribofuranosyl)-1,2,4-triazolin-5-one (**26**).

Attempts to utilize 3-nitro-1,2,4-triazolin-5-one[19] *via* trimethylsilylation and alkylation in the synthesis of **26** were unsuccessful. It would appear from these and related studies in the pyrimidine ring[30,31] that electron-withdrawing substituents hinder direct glycosylation by reducing the electron density of the pyrimidine type nitrogen to the point where alkylation by the C_1 of the sugar does not readily occur. The fusion reaction, on the other hand, is favored by electron-withdrawing substituents since it is the triazole anion which is alkylated.

Experimental Section

Detection of components on SilicAR 7 GF (Mallinckrodt) and alumina HF 254 (Brinkmann) was by ultraviolet light and by a 10% sulfuric acid in ethanol spray followed by heating under an infrared lamp. Alumina suitable for chromatographic absorption was obtained from Merck and Co.

Trimethylsilyl derivatives of the 1,2,4-triazoles were prepared by the general procedure of Wittenburg.[13] The 1,2,4-triazoles were heated under reflux in an excess of hexamethyldisilazane with a catalytic quantity of ammonium sulfate under anhydrous conditions until complete solution was achieved and evolution of ammonia ceased. The excess hexamethyldisilazane was removed by distillation under diminished pressure and the residue (oil or crystalline solid) was used directly without further purification unless otherwise specified.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (4).—A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[32] from 20.2 g (0.040 mol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in acetonitrile (250 ml) was added to the trimethylsilyl derivative prepared from 4.4 g (0.044 mol) of urazole[33] and the resulting solution was kept for 3 days at room temperature. After removal of the solvent, ethanol was added to the residue and the crystalline **4** separated to yield 18.3 g (84%), mp 202–204°. Recrystallization of the product from ethyl acetate–ethanol provided pure material, mp 203–205°.

Anal. Calcd for $C_{28}H_{23}N_3O_9$: C, 61.65; H, 4.25; N, 7.70. Found: C, 61.55; H, 3.95; N, 7.66.

1-(β-D-Ribofuranosyl)urazole or 1-(β-D-Ribofuranosyl)-1,2,4-triazolidine-3,5-dione (3).—A solution of **4** (5.0 g) in methanol (100 ml) saturated at 0° with ammonia was kept at room temperature for 3 days in a pressure bottle. After removal of the solvent, water (30 ml) was added and the mixture was extracted with ethyl acetate (three 25-ml portions). Dowex 50 (H) was added to the solution to pH 3, the solution was filtered, and the solvent was removed. Coevaporation of the residue with ethanol gave 1.2 g (56%) of **3** analytically pure: mp 163–165°; $[\alpha]^{30}D$ −52.6° (*c* 1.0, water); pmr (D_2O) δ 5.52 (d, 1, $J_{1',2'}$ = 5.0 Hz, 1'-H).

Anal. Calcd for $C_7H_{11}N_3O_6$: C, 36.05; H, 4.76; N, 18.02. Found: C, 36.11; H, 4.85; N, 17.80.

2-Methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (8).—A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide from 25.2 g (0.050 mol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in acetonitrile (250 ml) was added to the trimethylsilyl derivative prepared from 6.3 g (0.055 mol) of 1-methylurazole.[16] After 3 days at room temperature the solvent was removed, ethanol was added to the residue, and the solution was evaporated to a syrup. The syrup was dissolved in chloroform and applied to a silica gel column (4.0 × 50 cm) packed in chloroform. The column was eluted with chloroform (1.5 l.) and 100-ml fractions were taken. Fractions 8–14 were combined and evaporated to dryness. The residue was crystallized from methanol to provide 21.5 g (77%) of **8**, mp 150–152°.

Anal. Calcd for $C_{29}H_{25}N_3O_9$: C, 62.25; H, 4.50; N, 7.51. Found: C, 62.51; H, 4.52; N, 7.44.

2-Methyl-1-(β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (11).—A solution of **8** (11.2 g) in methanol (200 ml) saturated at 0° with ammonia was kept at room temperature for 3 days in a pressure bottle. The solvent was removed, and the product was crystallized from ethanol to give 3.5 g of **11**. The filtrate was evaporated to dryness. Water (30 ml) was added to the residue, and the mixture was extracted with ethyl acetate (three 20-ml portions). The aqueous solution was evaporated to dryness, and the residue was crystallized from ethanol to give an additional 0.9 g (total yield, 90%) of **11**: mp 180–182°; $[\alpha]^{29}D$ −12.3° (*c* 1.0, water); pmr (D_2O) δ 3.25 (s, 3, 2-CH_3), 5.47 (d, 1, $J_{1',2'}$ = 6.0 Hz, 1'-H).

Anal. Calcd for $C_8H_{13}N_3O_6$: C, 38.87; H, 5.30; N, 17.00. Found: C, 38.82; H, 5.17; N, 16.78.

4-Methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (5).—The preparation of **5** was accomplished as for **4** to give 46%, mp 178–181°. Recrystallization of the product from ethyl acetate–ethanol provided pure material, mp 182–184°.

Anal. Calcd for $C_{29}H_{25}N_3O_9$: C, 62.25; H, 4.50; N, 7.51. Found: C, 62.12; H, 4.52; N, 7.32.

3-Methoxy-4-methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-5-one (6). Method 1.—Excess diazomethane in dimethoxyethane[34] was added to a solution of **5** (1.1 g) in dimethoxyethane, and the solution was kept at room temperature for 12 hr. After removal of the solvent, the product was crystallized from methanol to give 0.6 g (53%) of **6**, mp 162–163°.

Method 2.—Methylation of **4** (3.0 g) by the procedure of method 1 above afforded 1.7 g (54%) of **6**: mp 162–163°; pmr ($CDCl_3$) δ 3.08 (s, 3, 4-CH_3), 3.81 (s, 3, 3-*O*-CH_3), 6.25 (s, 1, $J_{1',2'}$ < 1 Hz, 1'-H).

Anal. Calcd for $C_{30}H_{27}N_3O_9$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.62; H, 4.65; N, 7.15.

3,5-Dimethoxy-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (7).—The filtrate from the methylation of **4** was evaporated to dryness, and the residue was dissolved in benzene and applied to an alumina column (2.0 × 25 cm) packed in benzene. The column was eluted with benzene (500 ml), and 50-ml fractions were taken. Fraction 4 was evaporated to dryness, and the residue was crystallized from methanol to give 0.1 g of **7**: mp 116–117°; pmr ($CDCl_3$) δ 3.84 (s, 3, 3-*O*-CH_3), 4.06 ppm (s, 3, 5-*O*-CH_3).

Anal. Calcd for $C_{30}H_{27}N_3O_9$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.89; H, 4.62; N, 7.18.

2,4-Dimethyl-1-(β-D-ribofuranosyl)-1,2,4-triazolidine-3,5-dione (10).—Methyl iodide (0.35 g, 2.5 mmol) and potassium carbonate (0.38 g, 2.8 mmol) were added to a solution of **5** (1.4 g, 2.5 mmol) in dimethylformamide (5 ml). The mixture was stirred at room temperature for 10 hr, then poured into chloroform (150 ml). The solution was filtered, and the filtrate was evaporated to dryness. Chloroform (30 ml) was added to the residue, and the mixture was extracted with water. The chloroform solution was dried over anhydrous magnesium sulfate and filtered. A small amount of **5** was removed by chromatography of this solution on an alumina column (1.5 × 35 cm) packed in chloroform. The column was eluted with chloroform (250 ml), and 25-ml

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fractions were collected. Fractions 3–7 were combined and evaporated to give 1.3 g of a homogeneous syrup. This material was debenzoylated by refluxing in methanol (25 ml) containing sodium methoxide (0.10 g) for 45 min. The solution was neutralized with Dowex 50 (H), filtered, and evaporated to dryness. The product was crystallized from ethanol–ethyl acetate to give 0.4 g (66%) of **10**, mp 115–117°.

Method 2.—Methylation of **8** (2.8 g) by the procedure of method 1 above provided 0.8 g (61%) of **10**: mp 115–117°; $[\alpha]^{28}D$ −17.1 (*c* 1.0, water); pmr (D_2O) δ 3.03 (s, 3, 4-CH_3), 3.23 (s, 3, 1-CH_3), 5.44 (d, 1, $J_{1',2'}$ = 6.0 Hz, 1′-H).

Anal. Calcd for $C_9H_{15}N_3O_6$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.18; H, 5.77; N, 16.03.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-2-methyl-1,2,4-triazolidine-3,5-dione (12).—A mixture of 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride[17] (7.8 g, 0.020 mol) and the trimethylsilyl derivative prepared from 2.5 g (0.022 mol) of 1-methylurazole was heated *in vacuo* (*ca.* 14 mm) in an oil bath at 110° for 15 min. The residue was dissolved in ethyl acetate (50 ml), and the solution was washed with aqueous sodium hydrogen carbonate and water. After drying over anhydrous magnesium sulfate, the ethyl acetate solution was filtered, and the filtrate was evaporated to dryness. The product was crystallized from methanol to provide 3.8 g (41%) of **12**, mp 166–168°.

Anal. Calcd for $C_{24}H_{25}N_3O_7$: C, 61.66; H, 5.39; N, 8.99. Found: C, 61.97; H, 5.36; N, 8.77.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-2-methyl-1,2,4-triazolidine-3,5-dione (13).—A solution of **12** (2.6 g) was deblocked with methanolic ammonia as in the case of (**14**) to give a product which was recrystallized from ethanol to yield 0.9 g (70%) of **13**: mp 166–167°; $[\alpha]^{30}D$ +17.6 (*c* 1.0, water); pmr (D_2O); δ 3.23 (s, 3, 2-CH_3), 5.87 (t, 1, $J_{1'-2',2''}$ = 7.1 Hz, 1′-H).

Anal. Calcd for $C_8H_{12}N_3O_5$: C, 41.56; H, 5.67; N, 18.18. Found: C, 41.34; H, 5.72; N, 17.99.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-1,2,-4-triazolidine-3,5-dione.—A mixture of 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride (11.7 g, 0.030 mol) and the trimethylsilyl derivative prepared from 3.3 g (0.33 mol) of urazole was heated *in vacuo* (*ca.* 14 mm) in an oil bath at 110° for 30 min. The residue was dissolved in ethyl acetate and ethanol, the solution was filtered, and the filtrate was evaporated to dryness. Crystallization of the product from ethyl acetate and ethanol provided 7.5 g of the desired product. The filtrate was evaporated to dryness, and the residue was dissolved in chloroform and applied to a silica gel column (3.0 × 55 cm) packed in chloroform. The column was eluted with chloroform (3 l.), chloroform–ethyl acetate (95:5, 1 l.), and chloroform–ethyl acetate (90:10, 5 l.); and 200-ml fractions were taken. Fractions 24–44 were combined and evaporated to dryness, and the residue was crystallized from ethyl acetate and ethanol to give an additional 1.8 g. The total yield was 67%. Recrystallization of the product from ethyl acetate and ethanol provided pure 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)urazole: mp 219–221°; pmr (DMSO-d_6) δ 6.07 (t, 1, $J_{1'-2',2''}$ = 7.0 Hz, 1′-H).

Anal. Calcd for $C_{23}H_{23}N_3O_7$: C, 60.92; H, 5.11; N, 9.27. Found: C, 60.66; H, 5.14; N, 9.14.

1-(2-Deoxy-β-D-ribofuranosyl)urazole or 1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-1,2,4-triazolidine-3,5-dione (14).—A solution of the blocked nucleoside (2.0 g) in methanol (50 ml) saturated at 0° with ammonia was kept at room temperature for 3 days in a pressure bottle. After removal of the solvent, water (20 ml) was added to the residue, and the mixture was extracted with ethyl acetate (three 15-ml portions). The aqueous solution was evaporated to dryness, and the product was crystallized from ethanol to give 0.53 g (55%) of **14**: mp 208–210° dec; $[\alpha]^{27}D$ −3.3° (c 1.0, water); pmr (DMSO-d_6) δ 5.61 (m, 1, line width 14 Hz, 1′-H).

Anal. Calcd for $C_7H_{11}N_3O_5$: C, 38.71; H, 5.11; N, 19.35. Found: C, 38.47; H, 5.07; N, 19.38.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-2,4-dimethyl-1,2,4-triazolidine-3,5-dione. Method 1.—Methyl iodide (0.28 g, 2.0 mmol) and the potassium carbonate (0.30 g, 2.2 mmol) were added to a solution of 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-1,2,4-triazolidine-3,5-dione (0.45 g, 1.0 mmol) in dimethylformamide (4 ml), and the mixture was stirred at room temperature for 12 hr. The mixture was then poured into chloroform (150 ml) with stirring, the solution was filtered, and the filtrate was evaporated to dryness. Chloroform (20 ml) was added to the residue, and the mixture was extracted with water. The chloroform solution was dried over anhydrous magnesium sulfate and filtered. The filtrate was evaporated to dryness, and the product was crystallized from ether and cyclohexane to provide 0.39 g (81%), mp 98–100°.

Method 2.—Methyl iodide (0.14 g, 1.0 mmol) and potassium carbonate (0.15 g, 1.1 mmol) were added to a solution of **12** (0.47 g, 1.0 mmol) in dimethylformamide (4 ml), and the mixture was stirred at room temperature for 12 hr. The product was obtained exactly as in method 1 to give 0.41 g (85%) of product: mp 98–100°; pmr ($CDCl_3$) δ 3.05 (s, 3, 4-CH_3), 3.18 (s, 3, 2-CH_3), 5.97 (t, 1, $J_{1'-2',2''}$ = 7.0 Hz, $H_{1'}$).

Anal. Calcd for $C_{25}H_{27}N_3O_7$: C, 62.36; H, 5.65; N, 8.73. Found: C, 62.60; H, 5.62; N, 8.82.

3-Nitro-1,2,4-triazole (16).—3-Amino-1,2,4-triazole (25.2 g) was added in portions to a solution of 90% hydrogen peroxide (32.4 ml) in trifluoroacetic acid (120 ml) maintained at 0–10°. The resulting solution was gradually warmed to 70°, then maintained at 70–80° by intermittent cooling for 4 hr. The solution was kept overnight at 0°, and the crystalline product was collected to give 9.8 g of **16**. The filtrate was evaporated to an oily residue which was triturated with ethyl acetate. The resulting solid material was collected and extracted with ethyl acetate in a Soxhlet extractor. The ethyl acetate solution provided an additional 5.5 g of **16** (total yield, 45%). Recrystallization of the product from ethanol provided pure material with mp 213–215° dec. The compound exhibited uv bands at $\lambda_{max}^{pH\ 1}$ 245 mμ (ε 4610), 215 (5600); $\lambda_{max}^{pH\ 11}$ 291 mμ (ε 5870), 230 (2570).

Anal. Calcd for $C_2H_2N_4O_2$: C, 21.06; H, 1.77; N, 49.12. Found: C, 20.80; H, 1.84; N, 49.35.

3-Bromo-5-nitro-1,2,4-triazole (20).—A solution of 3-nitro-1,2,4-triazole (**16**) (5.7 g, 0.050 mol), sodium hydroxide (2.0 g, 0.050 mol), and bromine (3.0 ml) in water (25 ml) was heated at 80° until the bromination was complete (15–20 hr) as shown by tlc (SilicAR 7GF, ethyl acetate developer). The solution was cooled, acidified to pH 3 with dilute hydrochloric acid, and extracted with ethyl acetate (four 50-ml portions). The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The product was crystallized from ethyl acetate and benzene to provide 8.6 g (89%) of **20** with mp 157–159°. The compound exhibited uv bands at $\lambda_{max}^{pH\ 1}$ 262 mμ (ε 3950); $\lambda_{max}^{pH\ 11}$ 301 mμ (ε 5980), 231 (3820).

Anal. Calcd for $C_2HBrN_4O_2$: C, 12.45; H, 0.52; Br, 41.41; N, 29.03. Found: C, 12.34; H, 0.56; Br, 41.03; N, 28.84.

5-Bromo-3-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole (21).—3-Bromo-5-nitro-1,2,4-triazole (**20**) (5.8 g, 0.030 mol) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (9.5 g, 0.030 mol) were thoroughly mixed in a mortar, then heated *in vacuo* (*ca.* 14 mm) in an oil bath at 150° for 30 min. The residue was dissolved in ether and cyclohexane and seeded to give 12.6 g (93%) of **21** with mp 88–90°. Recrystallization of the product from ether and cyclohexane provided pure material with mp 90–92°. Seed crystals were obtained by chromatography on silica gel with benzene–ethyl acetate (9:1).

Anal. Calcd for $C_{13}H_{15}BrN_4O_9$: C, 34.60; H, 3.35; Br, 17.71; N, 12.42. Found: C, 34.36; H, 3.41; Br, 17.62; N, 12.37.

5-Methoxy-3-nitro-1-(β-D-ribofuranosyl)-1,2,4-triazole (24).—5-Bromo-3-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole (**21**) (9.0 g, 0.020 mol) was added to a solution of sodium (0.58 g, 0.025 mol) dissolved in methanol (50 ml), and the resulting solution was stirred at room temperature for 2.5 hr. After neutralization with Dowex 50 (H), the solution was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in methanol, silica gel (20 g) was added to the solution, and the mixture was evaporated to dryness. The silica gel mixture was added to a dry-packed silica gel column (2.5 × 25 cm), and the column was eluted with chloroform (0.5 l.), ethyl acetate–chloroform (1:1, 0.5 l.), and ethyl acetate (1 l.). Fractions of 200 ml were collected, and fractions 4–7 were combined and evaporated to dryness. Crystallization of the product from ethyl acetate provided 3.8 g (69%) of **24**: mp 126–127°; $[\alpha]^{30}D$ −56.6° (*c* 1.0, water); pmr (D_2O) δ 4.17 (s, 3, *O*-CH_3), 5.80 (d, 1, $J_{1',2'}$ = 3.5 Hz, 1′-H).

Anal. Calcd for $C_8H_{12}N_4O_7$: C, 34.78; H, 4.38; N, 20.29. Found: C, 34.73; H, 4.57; N, 20.18.

5-Benzyloxy-3-nitro-1-(β-D-ribofuranosyl)-1,2,4-triazole (25).—A solution of **21** (4.5 g, 0.010 mol) in dry 1,2-dimethoxyethane (15 ml) was added to a solution of sodium (0.34 g, 0.015 mol) dissolved in benzyl alcohol (15 ml), and the mixture was stirred at room temperature for 3 hr. After neutralization with

Dowex 50 (H), the solution was filtered. Silica gel (25 g) was added to the filtrate, and the mixture was evaporated to dryness. The silica gel mixture was added to a dry-packed silica gel column (3.0 × 30 cm). The column was eluted with chloroform (1 l.) which removed benzyl alcohol and benzyl acetate, followed by chloroform–ethyl acetate (1:1, 0.5 l.) and ethyl acetate (1.5 l.); and 200-ml fractions were taken. Fractions 6–11 were combined and evaporated to dryness, and the product was crystallized from ethanol–benzene to give 1.4 g (40%) of **25** with mp 106–108°.

Anal. Calcd for $C_{14}H_{16}N_4O_7$: C, 47.73; H, 4.58; N, 15.90. Found: C, 47.85; H, 4.49; N, 15.77.

3-Amino-1-(β-D-ribofuranosyl)-1,2,4-triazolin-5-one (26).—A solution of **25** (0.50 g) in ethanol and 10% palladium-on-carbon catalyst (0.10 g) was shaken on a Parr hydrogenation apparatus at 45 psi for 3 hr at room temperature. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness. The residue was dissolved in methanol, and silica gel (5.0 g) was added to the solution. The mixture was evaporated to dryness, and the silica gel mixture was added to a dry-packed silica gel column (2 × 20 cm). The column was eluted with chloroform (0.2 l.), chloroform–ethyl acetate (1:1, 0.2 l.), ethyl acetate (0.2 l.), ethyl acetate–methanol (95:5, 0.5 l.), and ethyl acetate–methanol (90:10, 1 l.); 100-ml fractions were collected. Fractions 12–15 were combined and evaporated to dryness. The product was crystallized from methanol and ethanol to give 0.19 g (58%) of **26**: mp 167–169° dec; $[\alpha]^{27}D$ −91.0° (c 1.0, water).

Anal. Calcd for $C_7H_{12}N_4O_5$: C, 36.21; H, 5.21; N, 24.13. Found: C, 36.25; H, 5.22; N, 23.89.

3-Amino-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (23).—3-Bromo-5-nitro-1,2,4-triazole (**20**) (1.9 g, 0.010 mol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (5.0 g, 0.010 mol) were thoroughly mixed in a mortar, then heated *in vacuo* (*ca.* 14 mm) in an oil bath at 150° for 30 min. The residue was dissolved in ethyl acetate and evaporated to dryness. This syrup, crude 5-bromo-3-nitro-1-(2,3,5-tri-*O*-benozyl-β-D-ribofuranosyl)-1,2,4-triazole (**22**), was dissolved in ethyl acetate–ethanol (1:1, 50 ml). Sodium acetate (0.9 g) and 10% palladium-on-carbon catalyst (1.0 g) were added to the solution and the mixture was shaken on a Parr hydrogenation apparatus at 40 psi for 3 hr at room temperature. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness. Water (30 ml) was added to the residue, and the mixture was extracted with ethyl acetate (three 50-ml portions). The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. Crystallization of the product from ethanol provided 3.5 g (60%) of **23**, mp 124–126°.

Anal. Calcd for $C_{28}H_{24}N_4O_7$: C, 63.63; H, 4.58; N, 10.60. Found: C, 63.82; H, 4.49; N, 10.48.

3-Nitro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (17).—3-Nitro-1,2,4-triazole (**16**) (2.3 g, 0.020 mol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10.1 g, 0.020 mol) were thoroughly mixed in a mortar, then heated *in vacuo* (*ca.* 14 mm) in an oil bath at 190° with magnetic stirring for 30 min. After cooling the reaction mixture, the product was crystallized from ethyl acetate and ethanol to yield 9.8 g (88%) of **17**, mp 153–155°. Recrystallization of the product from ethyl acetate and ethanol provided pure material: mp 155–156°; pmr (DMSO-d_6) δ 6.84 (d, 1, $J_{1',2'}$ = 1.2 Hz, 1'-H), 9.18 (s, 1, 5-H).

Anal. Calcd for $C_{28}H_{22}N_4O_9$: C, 60.21; H, 3.97; N, 10.03. Found: C, 60.52; H, 4.14; N, 9.96.

3-Nitro-1-(β-D-ribofuranosyl)-1,2,4-triazole (18).—A solution of **17** (11.2 g) was refluxed in methanol (50 ml) containing sodium methoxide (0.10 g) for 45 min. The solution was neutralized with Dowex 50 (H) and filtered, and the solvent was removed. The product was crystallized from 2-propanol to give 4.0 g (82%) of **18**, mp 135–137°. Recrystallization of the product from 2-propanol provided pure material: mp 138–140°; $[\alpha]^{28}D$ −24.1° (*c* 1.0, water); pmr (D_2O) δ 6.09 (d, 1, $J_{1',2'}$ = 3.0 Hz, 1'-H), 8.82 (s, 1, 5-H).

Anal. Calcd for $C_7H_{10}N_4O_6$: C, 34.15; H, 4.09; N, 22.76. Found: C, 34.00; H, 4.03; N, 22.88.

3-Amino-1-(β-D-ribofuranosyl)-1,2,4-triazole (19). Method 1.—A solution of **23** in methanol (30 ml) saturated with ammonia at 0° was kept at room temperature for 3 days in a pressure bottle. The solvent was removed, and the product was crystallized from methanol and ethyl acetate to give 0.35 g (85%) of **19** with mp 145–146°.

Method 2.—3-Nitro-1-(β-D-ribofuranosyl)-1,2,4-triazole (**18**) (1.2 g) and 85% hydrazine (5.0 ml) were heated on a steam bath until evolution of nitrogen ceased (*ca.* 20 min). The solution was evaporated to dryness, and the product was crystallized from ethanol to yield 0.95 g (88%) of **19**: mp 145–146°; $[\alpha]^{30}D$ −52.4 (*c* 0.98, water); pmr (DMSO-d_6-D_2O) δ 5.62 (d, 1, $J_{1',2'}$ = 4.0 Hz, 1'-H), 8.29 (s, 1, 5-H).

Anal. Calcd for $C_7H_{12}N_4O_4$: C, 38.89; H, 5.59; N, 25.92. Found: C, 38.75; H, 5.69; N, 25.82.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole.—A solution of 1-trimethylsilyl-1,2,4-triazole[35] (3.1 g, 0.022 mol) and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10.1 g, 0.020 mol) in acetonitrile (50 ml) was kept for 4 days at room temperature. The solvent was removed and the residue was dissolved in chloroform (30 ml). The chloroform solution was washed with dilute aqueous sodium hydrogen carbonate and water. After drying over anhydrous magnesium sulfate, the chloroform solution was filtered, and the volume was reduced to approximately 15 ml. This solution was applied to a silica gel column (3.5 × 60 cm) packed in chloroform. The column was eluted with chloroform (2 l.), and 200-ml fractions were taken. Fractions 5–8 were combined and evaporated to dryness, and the product was crystallized from ethanol to provide 5.6 g (54%) of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole with mp 103–105°.

Anal. Calcd for $C_{28}H_{23}N_3O_7$: C, 65.49; H, 4.51; N, 8.18. Found: C, 65.54; H, 4.45; N, 8.11.

1-(β-D-Ribofuranosyl)-1,2,4-triazole (15). Method 1.—A solution of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (5.1 g) in methanol (30 ml) containing sodium methoxide (0.10 g) was refluxed for 45 min. The solution was neutralized with Dowex 50 (H) and filtered, and the solvent was removed. The product was crystallized from methanol and ethyl acetate to give 1.8 g (90%) of **15**: mp 143–145°; $[\alpha]^{28}D$ −57.0° (c 1.0, water); pmr (DMSO-d_6) δ 5.85 (s, 1, $J_{1',2'}$ = 3.7 Hz, 1'-H), 8.06 (s, 1, 3-H), 8.80 (s, 1, 5-H).

Anal. Calcd for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.54; H, 5.59; N, 20.93.

Method 2.—A solution of sodium nitrite (0.15 g, 2.2 mmol) in water (3 ml) was added dropwise with stirring to a solution of 3-amino-1-(β-D-ribofuranosyl)-1,2,4-triazole (**19**) (0.43 g, 2.0 mmol) and 50% hypophosphorous acid (0.30 g) in water (5 ml) at room temperature. After 30 min the solution was evaporated to dryness. Methanol and silica gel (2.0 g) were added to the residue, and the mixture was evaporated to dryness. The silica gel mixture was added to a dry-packed silica gel column (1.5 × 20 cm), and the column was eluted with chloroform (0.1 l.), ethyl acetate–chloroform (1:1, 0.2 l.) and ethyl acetate (0.2 l.); 50-ml fractions were taken. Fractions 8 and 9 were evaporated to dryness, and the residue was crystallized from methanol and ethyl acetate to give 0.18 g (45%) of **15**.

Method 2 was repeated with 50% D_3–hypophosphorous acid in D_2O and with D_2O in place of water. The 50% D_3–hypophosphorous acid solution was prepared as follows. The water was removed from 50% hypophosphorous acid *in vacuo*, D_2O was added, and the evaporation was repeated. Sufficient D_2O was then added to make an approximately 50% D_3–hypophosphorous acid solution. The pmr spectrum of the product obtained was identical with that of **15** except that the signal for the 3-H at δ 8.06 integrated for 0.27 proton.

Registry No.—**3**, 24806-83-5; **4**, 24854-62-4; **5**, 24806-84-6; **6**, 24806-85-7; **7**, 24806-86-8; **8**, 24806-87-9; **10**, 24806-88-0; **11**, 24806-89-1; **12**, 24806-90-4; **13**, 24806-91-5; **14**, 24806-92-6; **15**, 24806-93-7; **16**, 24807-55-4; **17**, 24806-94-8; **18**, 24806-95-9; **19**, 24806-96-0; **20**, 24807-56-5; **21**, 24806-97-1; **23**, 24806-98-2; **24**, 24806-99-3; **25**, 24807-00-9; **26**, 24807-01-0; 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-1,2,4-triazolidine-3,5-dione, 24807-02-1; 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-2,4-dimethyl-1,2,4-triazolidine-3,5-dione, 24807-03-2; 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole, 24807-04-3.

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Aluminum Chloride Catalyzed Reaction between *t*-Butylbenzene and Phosphorus Trichloride[1]

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The reaction of *t*-butylbenzene with phosphorus trichloride in the presence of aluminum chloride gives *p*-*t*-butylphenyl-*t*-butylphosphinic acid after hydrolysis of the phosphinyl chloride, which is a reaction intermediate. Small amounts of phenyl-*t*-butylphosphinic acid were isolated in some of the reactions. The mass spectra of these compounds were examined.

The reaction between *t*-butylbenzene and phosphorus trichloride in the presence of aluminum chloride, followed by treatment with chlorine, and then with ethanol, and then with aqueous hydrochloric acid, is reported to give a mixture of *p*-*t*-butylphenylphosphonic acid (I) and di-*p*-*t*-butylphenylphosphinic acid (II).[3] The overall yields were low because of isolation and purification problems.

We attempted to follow the original procedure given by Kosolapoff but were unable to isolate either I or II and obtained *p*-*t*-butylphenyl-*t*-butylphosphinic acid (III) in *ca.* 20% yield (based on *t*-butylbenzene) which we assume was formed by reactions between an aryl group, a *t*-butyl cation or isobutene, and a trivalent phosphorus compound. A possible reaction scheme is shown in Scheme I. (In Schemes I and II possible addition complexes between *t*-butylbenzene and aluminum and phosphorus chloride are not shown, and these schemes therefore represent oversimplified minimum descriptions.)

In addition to III a small amount of phenyl-*t*-butylphosphinic acid (IV) was sometimes formed, either by dealkylation of one of the precursors of III or by a reaction of benzene, generated for example by dealkylation of *t*-butylbenzene. The maximum amount found was *ca.* 5% of that of III. A possible reaction sequence is shown in Scheme II. The particular sequences of reactions shown in Schemes I and II are assumed; *e.g.*, the dealkylation could follow an initial reaction with PCl_3.

Reactions between trivalent phosphorus and electrophiles[4] and dealkylations of alkylbenzenes by Lewis acids[5] are well known. There appeared to be no role for chlorine in these reactions and therefore we repeated the experiments omitting the addition of chlorine, followed by ethanol and acid hydrolysis, as in Kosolapoff's original procedure,[3] and we isolated the phosphinyl chloride (V) which was subsequently hydrolyzed in alkali to the acid III.

The reaction which we observe provides a simple single-step procedure for the synthesis of alkylarylphosphinic acids,[3,6,7] although the scope of the reaction needs to be explored. It seems that the original procedure using phosphorus trichloride and aluminum chloride is not always satisfactory for the synthesis of phosphonic acids.[3]

Experimental Section

Materials.—Phosphorus trichloride (B and A) was redistilled and aluminum chloride (B and A) was sublimed *in vacuo*. *t*-Butylbenzene (MCB) was shown by glc to contain <0.1% benzene.

Reaction Conditions.—The first experiment was done following the original procedure of Kosolapoff,[3] with PCl_3 (270 g), $AlCl_3$ (45 g), and *t*-butylbenzene (67 g). The materials were refluxed for 4 hr and the volatiles, including PCl_3, were distilled off. 1,1,2,2-Tetrachloroethane (200 ml) was then added and the solution was saturated with chlorine. Ethanol (146 ml) was added dropwise at 15° giving amounts of HCl gas. The mixture was treated with ice and then concentrated HCl. The organic layer was washed with water and saturated salt solution and dried over anhydrous $MgSO_4$. The solvent was then evaporated to give an oil which solidified on standing. According to the original procedure, the esters of the phosphonic and phosphinic acids should have been sufficiently volatile to be distilled *in vacuo*, but we obtained no distillate and therefore refluxed the nonvolatile material with concentrated HCl, as described.[3] A white solid, sparingly soluble in cold H_2O, was obtained. Extraction of this solid with hot water and subsequent evaporation of water gave a white crystalline solid which after several recrystallizations from 50:50 H_2O–EtOH had mp 154–156°. This solid was shown to be phenyl-*t*-butylphosphinic acid (IV).

The bulk of the material was not extracted into hot water but was recrystallized several times from a 50:50 H_2O–EtOH solution giving solid white crystalline needles, mp 208–209°. This solid was shown to be *p*-*t*-butylphenyl-*t*-butylphosphinic acid (III), obtained in 20% yield. Considerable amounts of material were probably lost in the recrystallizations.

Neither of these acids had the properties of *p*-*t*-butylphenylphosphonic acid (mp 199–200°) or di-*p*-*t*-butylphenylphosphinic acid (mp 211–212°).[3]

The reaction was repeated on half the original scale omitting the addition of chlorine and the refluxing with concentrated HCl. The initial product formed after removal of the volatile materials was an oil which solidified on standing, yielding the white solid V, 14 g (23% yield). Recrystallization from petroleum ether gave *p*-*t*-butylphenyl-*t*-butylphosphinyl chloride (mp 116–118°). It was identified by comparison of its 60-MHz nmr spectrum with that of material prepared from the phosphinic acid and thionyl chloride,[7] and by chloride analysis. Hydrolysis of the crude chloride in alkali gave much less phenyl-*t*-butylphosphinic acid (IV) than in the original experiment, and the major product was *p*-*t*-butylphenyl-*t*-butylphosphinic acid (III). In another preparation, $AlCl_3$ was used without sublimation and the same phosphinic acids were formed. The isolation of the chloride V depends on the extent of hydrolysis during isolation, and the formation of the acid IV depends fortuitously upon the reaction conditions, *e.g.*, upon the extent to which the $AlCl_3$ catalyzes the dealkylation relative to the Friedel–Crafts reaction.

In order to determine the possibility that phenyl-*t*-butylphosphinic acid (IV) was formed by a loss of a *t*-butyl group from a *p*-*t*-butylphenyl-*t*-butylphosphinyl derivative, we heated 5 g of III with $AlCl_3$ (8 g) and PCl_3 (50 ml) for 2 hr under reflux, but found none of the acid IV. This experiment suggests that alkyl cleavage precedes formation of the acid III.

Evidence for Structure.—*p*-*t*-Butylphenyl-*t*-butylphosphinic

(1) Support of this work by the National Institute of Arthritis and Metabolic Diseases of the USPHS is gratefully acknowledged.

(2) To whom inquiries should be addressed.

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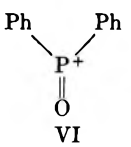
acid (III), mp 208–209°, is a monobasic acid (molecular weight by neutralization 252). *Anal.* Calcd for $C_{14}H_{23}O_2P$: C, 66.1; H, 9.1; P, 12.2. Found: C, 66.6; H, 8.6; P, 12.3.

The mass spectrum has a parent peak P = 254, and the nmr spectrum in $CDCl_3$ (60 MHz) gave a doublet, δ 0.90 and 1.16 (9, J = 16 Hz), 1.31 (9), a multiplet, δ 7.58 (9), and a singlet, δ 12.10 (1). (The relative areas are shown in parentheses.) The latter peak is that of the ionizable hydrogen and disappears on treatment with D_2O in CH_3CN. The infrared spectrum (Nujol mull or KBr pellet) showed peaks at 9.0, 11.5–12.5 μ which are characteristic of 1,4-disubstituted phenyl compounds.[8]

Phenyl-*t*-butylphosphinic acid (IV), mp 154–156°, is a monobasic acid. *Anal.* Calcd for $C_{10}H_{15}O_2P$: C, 60.6; H, 7.7; P, 15.7. Found: C, 60.6; H, 7.8; P, 15.9. The nmr spectrum in $CDCl_3$ (60 MHz) gave a doublet, δ 0.90 and 1.17 (9), multiplet, δ 7.57 (5), and a singlet, δ 11.6 (1). (The relative areas are shown in parentheses.) The latter peak is that of the ionizable hydrogen and disappears after treatment with D_2O. The proton phosphorus nmr coupling is well established from work on compounds containing alkyl groups attached to phosphorus.[7,9] Siddall and Prohaska have studied the nmr of IV and its chloride and report a coupling constant J = 15.7 Hz for the acid and J = 17.7 Hz for the chloride.[7] (They reported no other physical properties for these compounds.)

The phosphinyl chloride V had mp 116–118° (found Cl, 12.9% by Ag titration; calcd Cl, 13.0%). The mass spectrum has parent peaks P = 272 (^{35}Cl) and P = 274 (^{37}Cl). The nmr spectrum (60 MHz in CCl_4) is very similar to that of III and the peaks were a doublet δ 1.06 and 1.36 (9), 1.35 (9), and a multiplet, δ 7.5 (4). A coupling constant J = 17 Hz was found in agreement with the results of Siddall and Prohaska.[7]

The mass spectra (MS 902, 70 eV) of these compounds are quite different from the spectra observed by Haake and his coworkers for diarylphosphinic acids[10] and related compounds, in that there is no evidence for VI or ions derived from it.

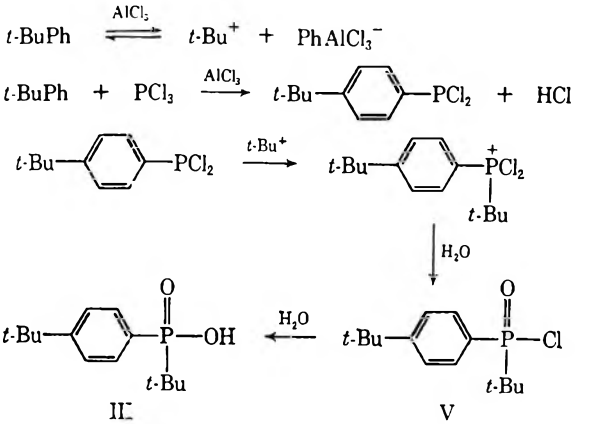


VI

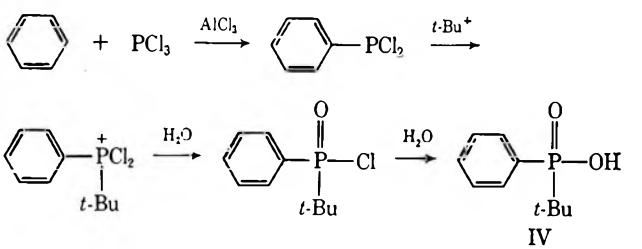
Results

Mass Spectra.—The principal peaks of the mass spectrum of *p*-*t*-butylphenyl-*t*-butylphosphinic acid, with their sizes relative to the base peak 198 are 256 (2), 255 (21), 254 (33), 239 (9), 199 (19), 198 (100), 197 (8), and 183 (40%). There are metastable ions at 169 and 154 which correspond to the transition 198 → 183 and 254 → 198, respectively. In agreement with the results of Haake and coworkers,[10] we find a large M + 1 peak and a large peak which could be formed by loss of isobutene from the molecular ion. Existing evidence suggests that isobutene is lost from the *t*-butyl group attached to phosphorus; a *t*-butyl cation could also be lost from the P + 1 ion. This reaction is also observed with phenyl-*t*-butylphosphinic acid. These reactions in the ion source are analogous to the reverse reaction of attack of the *t*-butyl cation upon a trivalent phosphorus compound in the synthesis of these phosphinic acids. Scheme III accounts for the mass spectrum.

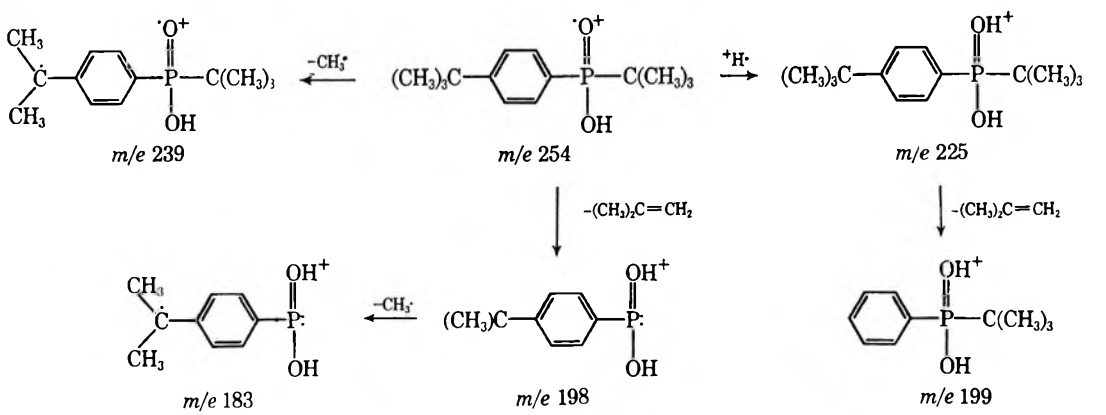
Scheme I



Scheme II



Scheme III



The principal peaks of the mass spectrum of phenyl-*t*-butylphosphinic acid with their sizes relative to the base peak 142 are 200 (0.3), 199 (3), 198 (13), 183 (1.2), 143 (6), and 141 (3%). The metastable ion at 101.8 corresponds to the transition 198 → 142. Scheme IV accounts for the observed spectrum.

The nmr spectra and these mass spectra, together with the results of Haake and his coworkers on the mass

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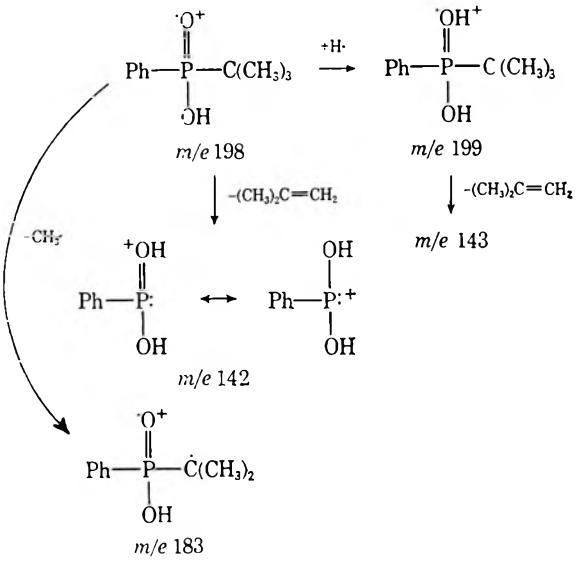
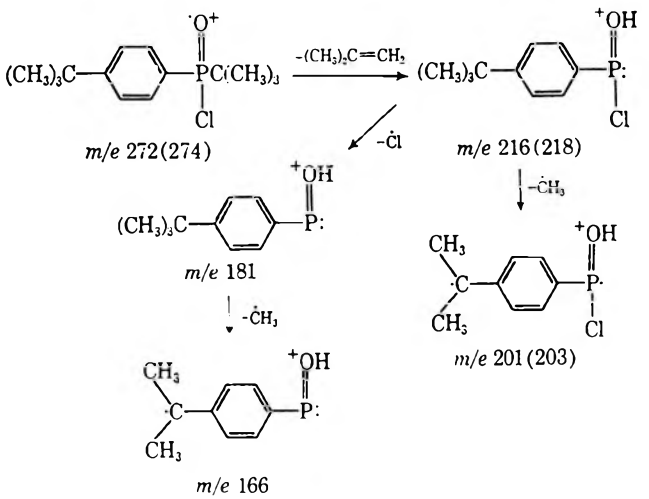
SCHEME IV



SCHEME V[a]



[a] The mass numbers in parenthesis denote the ion containing ^{37}Cl.

spectra of diarylphosphinic acids,[10] confirm that we isolated arylalkylphosphinic acids and not the compounds originally reported.[3]

The principal peaks of the mass spectrum of *p*-*t*-butylphenyl-*t*-butylphosphinyl chloride with sizes relative to the base peak 216 are 274 (11), 272 (30), 218 (43), 203 (24), 201 (83), 181 (6), and 166 (4%). Metastable ions are observed at 189, 187 with a broad peak at 171.8, and correspond to the transitions 218 → 203, 216 → 201 and 272 → 216, and 274 → 218, respectively. Scheme V illustrates this pattern.

Registry No.—III, 25097-42-1; IV, 4923-86-8; V, 25097-44-3; aluminum chloride, 7446-70-0; *t*-butylbenzene, 98-06-5; phosphorus trichloride, 7719-12-2.

Conformation of the Sodium Salts of 4-Phenylbutyric Acid and ω-Phenyloctanoic Acid in Aqueous Solution

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The conformations of the sodium salts listed in the title have been investigated in deuterium oxide by nuclear magnetic resonance spectroscopy. The conformation of 4-phenylbutyric acid sodium salt has been found to exist in the *anti* form with respect to the β,γ carbon–carbon bond. The data do not permit the establishment of a unique conformation for sodium ω-phenyloctanoate, but possible conformations are delineated.

The nature and extent of the intermolecular and the intramolecular interaction of two or more apolar moieties in water continues to be a subject of extensive and lively investigation.[2-11] The elucidation of these interactions is crucial to an understanding of molecular conformations and reaction mechanisms in aqueous solution.

Over the past few years many investigators have examined the nature, structure, and the effect on reactivity of micelles.[5,7,12-15] However, the conformations of the molecular constituents of micelles have received relatively little attention. It has been fairly well established in a number of cases that at concentrations below the critical micelle concentration (cmc), intermolecular association can occur.[6,16] We have initiated a study of ω-phenylalkylcarboxylic acid salts in aqueous solution with the goal of obtaining information regarding the conformations of the anions at concentrations below the cmc. Our approach makes use of the phenyl ring as a conformational probe. The magnetic anisotropy arising from the ring current of the phenyl ring will affect the chemical shifts of any protons located in the

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(10) D. S. Olander and A. Holtzer, *J. Amer. Chem. Soc.*, **90**, 4549 (1968).
(11) M. P. Schweizer, A. D. Broom, P. O. P. Ts'O, and D. P. Hollis, *ibid.*, **90**, 1042 (1968).
(12) R. Haque, *J. Phys. Chem.*, **72**, 3056 (1968).
(13) R. B. Dunlap and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 4395 (1968), and references cited therein.
(14) L. R. Romsted and E. H. Cordes, *ibid.*, **90**, 4404 (1968).
(15) F. M. Menger and C. E. Portnoy, *ibid.*, **90**, 1875 (1968).
(16) P. Mukerjee, K. J. Mysels, and C. I. Dulin, *J. Phys. Chem.*, **62**, 1390 (1958).

TABLE I

CHEMICAL SHIFTS OF THE ACIDS IN DEUTERIUM OXIDE AND CARBON TETRACHLORIDE

Compd	Solvent (pD)	Concn, M[b]	Chemical shifts, ppm[a] $-C_6H_5$	$-CH_2C_6H_5$	$-CH_2-C(=O)$	$-CH_2-$	CH_3
Propionic acid	D_2O (1.6)	1.4×10^{-1}			2.40		1.08
	D_2O (9.8)	6×10^{-2}			2.17		1.04
	CCl_4	0			2.34[c]		1.14[c]
4-Phenylbutyric acid	D_2O (9.0)	1×10^{-1}	7.34	2.65	2.20	1.93	
	D_2O (9.4)	6×10^{-2}	7.33	2.64	2.21	1.91	
	D_2O (9.8)	2×10^{-2}	7.34				
	CCl_4	0	7.15[c]	2.67[c]	2.32[c]	2.07[c]	
Octanoic acid	D_2O (8.9)	1×10^{-1}			2.16	~1.3	0.85
	D_2O (9.1)	6×10^{-2}			2.17	~1.3	0.85
	D_2O (9.5)	2×10^{-2}			2.15	~1.3	0.84
	CCl_4	0			2.32	~1.3	0.89
ω-Phenyloctanoic acid	D_2O (8.5)	1×10^{-1}	7.05	2.43	2.15	~1.3	
	D_2O (8.6)	6×10^{-2}	7.11	2.47	2.14	~1.3	
	D_2O (9.2)	2×10^{-2}	7.31	2.64	2.12	~1.3	
	CCl_4	0	7.11[c]	2.57[c]	2.30[c]	~1.4	

[a] Based on first-order analysis and estimated to be reproducible to ± 0.02 ppm. TMS and DSS were used as internal references in CCl_4 and D_2O, respectively. [b] Zero values correspond to infinite dilution. [c] Value obtained from a plot of concentration *vs.* chemical shift extrapolated to infinite dilution.

vicinity of the ring.[17,18] If intramolecular hydrophobic (or hydrotactoid) forces are strong enough, the ω-phenylalkyl moiety of a sodium ω-phenylalkylcarboxylate may assume a conformation in which the distance between the phenyl ring and the carbon atom α to the carboxylate group is less than the theoretical distance of maximum extension.[8] Two nmr methods have been employed to examine this possibility. The first approach (method 1) involves the determination of the nuclear magnetic resonance spectra of the ω-phenylalkylcarboxylic acids (specifically 4-phenylbutyric acid and ω-phenyloctanoic acid) at infinite dilution in CCl_4 where, since hydrophobic bonding is not possible, the hydrocarbon moiety will assume a more or less extended conformation.[8] The spectra are then compared, with respect to the chemical shifts of the methylene protons (especially the protons α to the carboxyl group), with the spectra of the sodium salts of the acids in D_2O. A correction to the proton chemical shift resulting from salt formation is estimated by noting the effect of converting propionic acid to its sodium salt on the α-proton resonances. Now if the α-methylene protons are indeed located in the near vicinity (6–8 Å or less) of either the shielding or deshielding regions of the phenyl ring, then the observed chemical-shift difference $\Delta\delta_{CCl_4-D_2O}$ for the phenyl-substituted acid and its sodium salt should be significantly different ($\geq$ 0.1 ppm) from $\Delta\delta'_{CCl_4-D_2O}$, the shift difference for propionic acid and its sodium salt. If the protons lie in or very near the region where the diamagnetic and paramagnetic effects exactly cancel one another or if the protons are farther than 6–8 Å from the phenyl ring, then one would expect a shift difference ($\Delta\delta_{CCl_4-D_2O} - \Delta\delta'_{CCl_4-D_2O}$) of 0.0 ± 0.1 ppm. Method 2 is based on the direct comparison of the phenylalkylcarboxylic acid salts in D_2O with sodium propionate. Assuming that sodium propionate is a good choice for a reference compound, this method should yield shift data similar to method 1 data.

Results

The chemical-shift data for the various acids and their sodium salts in CCl_4 and D_2O are summarized in Table I. Propionic acid, which has a relatively simple nmr spectrum, was chosen as the model compound for determining the effect of solvent (CCl_4 and D_2O) and pD on the chemical shift of the protons α to the carboxyl group. In addition, propionic acid should exhibit (in the nmr at room temperature) no conformational changes as the solvent is varied. Klevens has determined the critical micelle concentration of a number of potassium salts of aliphatic carboxylic acids.[19] At 25° the cmc of the C_6 carboxylate was 1.55 M, 0.098 M for the C_{10} salt, and 0.0255 M for the C_{12} salt. These data suggest that the concentrations listed in Table I for the sodium salts of propionic acid and 4-phenylbutyric and octanoic acid in D_2O are below the critical micelle concentrations of the respective salts. Further evidence bearing on this point is provided by the chemical shift of the aromatic protons of the phenyl-substituted salts. The chemical shift of the phenyl protons of ω-phenyloctanoate in D_2O at a concentration of 2×10^{-2} M (pD 9.2) was 7.31 ppm (Table I), which shifted 0.20 ppm upfield (to 7.11 ppm) when the salt concentration was increased to 6×10^{-2} M (pD 8.6). Similar phenyl proton shifts (with respect to direction and magnitude) have been observed for a series of ω-phenylalkyltrimethylammonium bromides when the cmc was reached upon increasing the bromide concentration.[20] The chemical shift of the phenyl protons of 4-phenylbutyrate in D_2O showed virtually no change over the concentration range of 1×10^{-1} to 2×10^{-2} M (Table I). However, the chemical shift of the phenyl protons of ω-phenyloctanoate at the lowest concentration (2×10^{-2} M, D_2O) examined and the shift of the aromatic protons of 4-phenylbutyrate at all concentrations measured, in D_2O, yielded essentially the same values (7.31 ppm for ω-phenyloctanoate and 7.34 ppm for 4-phenylbutyrate, Table I). These results indicate

(17) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(18) J. W. Emsley, J. Feeney and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, p 595.

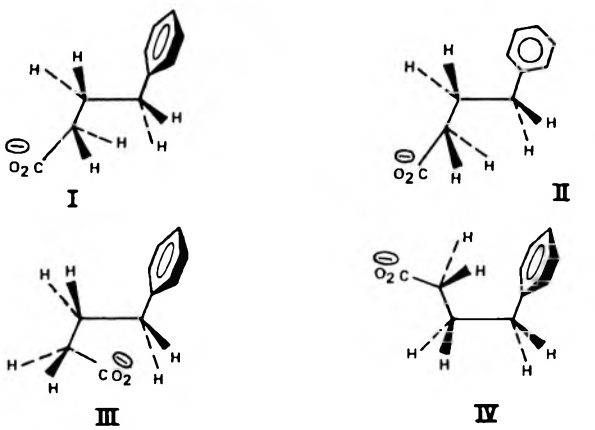
(19) H. B. Klevens, *J. Phys. Chem.*, **52**, 130 (1948).

(20) H. Inoue and T. Nakagawa, *ibid.*, **70**, 1108 (1966), and references cited therein.

that 2×10^{-2} M sodium ω-phenyloctanoate in D_2O and 2×10^{-2} to 1×10^{-1} M sodium 4-phenylbutyrate are below their respective critical micelle concentrations under the conditions studied.

Discussion

Consider first the preferred conformation of sodium 4-phenylbutyrate in D_2O. Conformers I–IV represent limiting conformations of this acid salt as determined from Corey–Pauling–Koltum (CPK) molecular models



and consideration of the calculated effect of the relative orientation of the phenyl ring, with respect to the aliphatic protons, on the chemical shifts of the α and β protons. Another possibility is that two or more conformers may be in equilibrium with one another. The shift of the α-proton resonance resulting from the magnetic anisotropy of the phenyl ring is estimated (from the data presented in Tables II and III) to be −0.04 to −0.06 ppm. For conformer I, the Johnson–Bovey tables[18] predict that the phenyl ring should cause a shift of the α protons of − 0.144 ppm; for II, a shift of −0.153 ppm; for III, a shift of −0.035 ppm; and finally, for IV, a shift of 1.46 ppm is calculated. The average error between the shifts observed by Johnson and Bovey[17] for various phenyl derivatives and the calculated values was 0.07 ppm (the actual error values ranged from 0.01 to 0.15 ppm). Hence, the observed shift for the α protons of sodium 4-phenylbutyrate (−0.04 to −0.06 ppm) rules out only conformer IV as a significant contributor to the preferred conformation of sodium 4-phenylbutyrate. Since conformer IV allows the maximum apolar interaction possible (as determined from CPK models), it is concluded that hydrophobic (or hydrotactoid) forces are not the predominant forces determining the conformation of sodium 4-phenylbutyrate.

Table II

α-Proton Shifts Relative to Sodium Propionate[a]

Compd	Concn, M	pD	Shift,[b] ppm
4-Phenylbutyric acid	6×10^{-2}	9.8	−0.04
Octanoic acid	2×10^{-2}	9.5	+0.02
ω-Phenyloctanoic acid	2×10^{-2}	9.2	+0.05

[a] Concentration 6×10^{-2} M, pD 9.8, DSS internal reference. [b] Positive sign indicates upfield shifts relative to the α protons of sodium propionate.

Table III

α-Proton Shifts ($\Delta\delta_{CCl_4-D_2O}$) of the Acids

Compd	Solvent (pD)	Concn, M[a]	$\Delta\delta_{CCl_4-D_2O}$[b]
Propionic acid	CCl_4	0	
	D_2O (9.8)	6×10^{-2}	+0.17
4-Phenylbutyric acid	CCl_4	0	
	D_2O (9.4)	6×10^{-2}	+0.11
Octanoic acid	CCl_4	0	
	D_2O (9.5)	2×10^{-2}	+0.17
ω-Phenyloctanoic acid	CCl_4	0	
	D_2O (9.2)	2×10^{-2}	+0.18

[a] Zero values correspond to infinite dilution. [b] In parts per million; individual chemical shifts were taken from Table I. Positive sign indicates an upfield shift.

The observed chemical shift of the β protons of 4-phenylbutyric acid in CCl_4 (at infinite dilution) minus the chemical shift of the salt in D_2O (6×10^{-2} M) yields a shift difference of 0.16 ppm (see Table I). From the data listed for propionic acid in Table I the effect of salt formation on the β-proton resonances is estimated to be 0.10 ppm. Therefore, the observed shift due to the phenyl's influence on the β protons is approximately 0.06 ppm. The predicted shift (from the Johnson–Bovey tables) due to the phenyl's influence of the β protons in conformer I (and III) is estimated to be 0.065 ppm; the predicted shift of the β protons in conformer II is −0.380 ppm. Therefore, the β-proton data exclude conformer II. Clearly, the shift data presented so far exclude conformers II and IV as significant contributers to the average conformation of sodium 4-phenylbutyrate. These data do not exclude I, III, or I $\rightleftharpoons$ III. However, CPK models indicate that there is considerable steric interaction between the carboxylate carbon atom and the benzylic protons in conformer III. The models also suggest the possibility of steric inhibition to solvation of the carboxyate moiety for this conformer. It is therefore concluded that conformer I best represents the preferred conformation of sodium 4-phenylbutyrate.

The shifts of the α protons of ω-phenyloctanoic acid determined by methods 1 and 2 are 0.01 and 0.05 ppm, respectively. If octanoic acid is used as the model compound in method 2, the shift obtained is +0.03 ppm. Figure 1 shows the ±0.10 ppm limits which define that region of space the α protons may occupy, with respect to the center of the phenyl ring, and still yield shifts consistent with the observed data. Unfortunately, the extended form of the acid salt and a conformation which allows the α protons to approach to within 2.9 Å of the phenyl ring (determined from Corey–Pauling–Koltun models) are both consistent with the observed shifts and consequently, within the limits previously delineated, no concrete conclusions regarding the major conformers of this acid salt can be supplied.

The use of sodium 4,4-dimethyl 4-silapentane-1-sulfonate (DSS) as an internal standard in aqueous solutions containing aromatic solutes and/or micelles has been criticized.[20,21] However, 4-phenylbutyric acid in D_2O showed virtually no change in the phenyl proton chemical shift over the concentration range of 1×10^{-1} M to 2×10^{-2} M (Table I). The studies[21] which demonstrated that the DSS signal could be shifted in aqueous solution by the presence of aromatic solutes involved an aromatic solute concentration of 0.8 M and a DSS concentration of 1.5–3.0 wt %. The salt concen-

(21) E. S. Hand and T. Cohen, *J. Amer. Chem. Soc.*, **87**, 133 (1965).

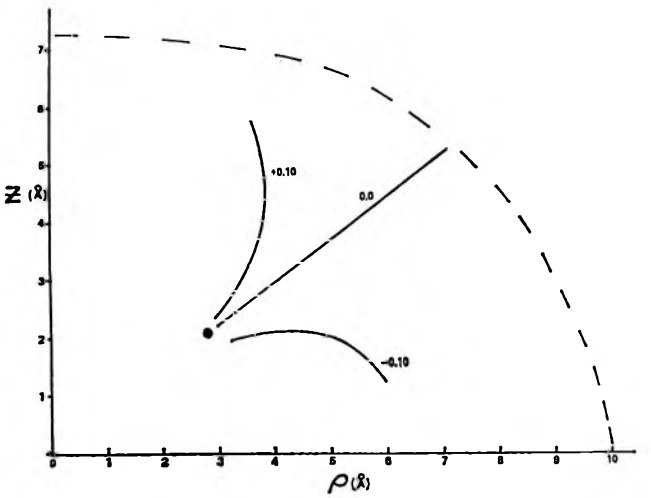


Figure 1.—The +0.10-, 0.00-, and −0.10-ppm isoshielding lines about a phenyl ring. Z is the axis perpendicular to the phenyl nuclear plane and passing through the center of the ring, and ρ is the axis perpendicular to Z and passing through the center of the phenyl ring. The dotted line represents the maximum possible distance of the α protons of sodium ω-phenyloctanoate from the center of the phenyl ring. The origin is at the center of the phenyl ring. The point on the graph represents the distance of closest approach of the α protons to the phenyl ring.

trations listed in Table I are considerably lower than 0.8 *M;* the DSS internal reference constituted no more than 1% by weight of the D_2O solutions used (Table I). The downfield shift of the phenyl protons of ω-phenyloctanoic acid sodium salt (Table I) upon dilution is opposite to that expected if DSS complexed with the carboxylate salt. All of these considerations suggest that the chemical shifts listed in Table I are real and do not reflect a perturbation of the DSS resonance position.

Experimental Section

Proton magnetic resonance spectra were obtained on a Jeolco C-60H nmr spectrometer operating at 60 MHz with an ambient probe temperature of approximately 29°. Tetramethylsilane (TMS) was used as an internal reference in carbon tetrachloride solutions and sodium 4,4-dimethyl 4-silapentane-1-sulfonate (DSS) was used as an internal reference in D_2O solutions. Chemical shifts were found to be reproducible to within ±0.02 ppm. Chemical shifts were estimated by first-order analyses and are believed to be accurate to <0.1 ppm. The D_2O solutions were 0.2 *M* in NaCl. The listed pD values are the readings obtained directly from the pH meter.

Materials.—Solvents and internal reference compounds were obtained from Nuclear Magnetic Resonance Specialties, Inc. Propionic acid (Baker Analyzed reagent), 4-phenylbutyric acid (Eastman), and ω-phenyloctanoic acid (Pfaltz and Bauer) were used without further purification. Octanoic acid (Matheson Coleman and Bell) was distilled under reduced pressure, bp 83–85° (0.25 mm).

Registry No.—4-Phenylbutyric acid sodium salt, 1716-12-7; sodium ω-phenyloctanoate, 24867-14-9.

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An Efficient Synthesis of Selected Indenones

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An efficient, apparently general synthesis of 2-alkylindenones is described. This procedure is dependent on the Friedel–Crafts acylation of α-alkyl-β-aryl-β-chloropropionyl chlorides (**5**) to furnish 2-alkyl-3-chloroindanones (**6**), dehydrochlorination of which affords the 2-alkylindenones (**7**). The method is also applicable to the preparation of indenone **7a**. The requisite acid chlorides **5** are prepared by the action of thionyl chloride on β-arylhydracrylic acids **4**, the esters of which are available conveniently by application of the Reformatsky procedure to the appropriate benzaldehyde **1** and α-bromo ester **2**. Selected examples of the reaction of the indenone system with electrophilic and nucleophilic reagents are presented. Isomerization of the alkylindenone system into the 2-alkylideneindanone system was noted to a small extent under certain conditions.

In the course of another investigation, we required a procedure for the synthesis of 2-alkylindenones. Several methods for their preparation have been reported, but none appeared to be uniformly general. Among the potential procedures, dehydrobromination of 2-alkyl-2-bromoindanones, available by bromination of the corresponding 2-alkylindanones, has been studied most extensively. Despite the apparent general nature of this sequence for the preparation of 2-methylindenones,[1] its applicability to the synthesis of higher homologs is questionable. Thus, dehydrobromination of 2-ethyl-2-bromoindanone affords a mixture of 2-ethylindenone and 2-ethylideneindanone, the latter predominating.[2] Yet, treatment of 2-bromo-2-butylindanone with dimethylamine is reported to give 2-butyl-3-dimethylaminoindanone, apparently *via* Michael addition of the amine onto the intermediate 2-butylindenone.[1a] Cyclization of *cis*-cinnamic acids is a second procedure that has been studied.[3] This method appears limited in that the *trans* isomer results from most syntheses, and conversion into the required *cis* isomer is not uniformly successful.[2,4]

Two additional methods for the preparation of 2-alkylindenones have received limited attention. Vilsmeier–Haack formylation of an acetophenone is reported to give a 3-amino-1-chloroindene, which was converted into a 2-methylindenone in two stages.[5] The general utility of this procedure has not been ascer-

(1) (a) S. Allisson, J. Büchi, and W. Michaelis, *Helv. Chim. Acta*, **49**, 891 (1966); (b) J. G. Topliss and L. M. Konzelman, *J. Pharm. Sci.*, **57**, 737 (1968).

(2) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1452 (1960).

(3) (a) R. Stoermer and G. Voht, *Justus Liebigs Ann. Chem.*, **409**, 36 (1915); (b) S. Goszczynski and E. Salwinska, *Zesz. Nauk. Politech. Slask., Chem.*, **24**, 235 (1964); *Chem. Abstr.*, **63**, 11415e (1965).

(4) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 448 (1968).

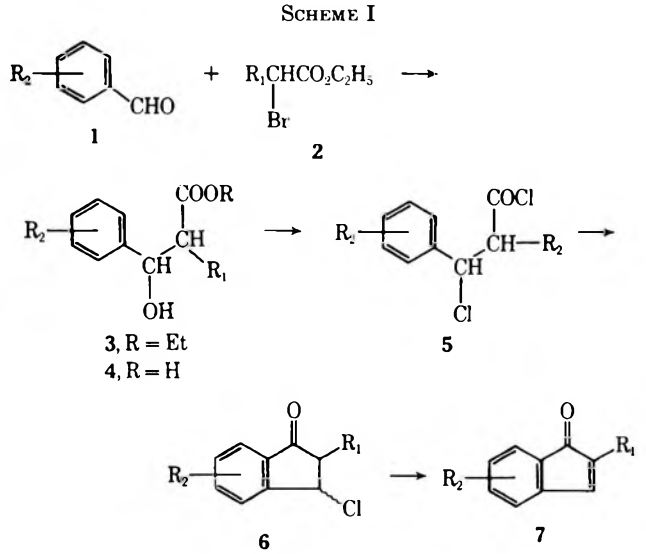
(5) K. Bodendorf and R. Mayer, *Chem. Ber.*, **98**, 3565 (1965).

tained. Secondly, bromination of β-(indanon-2-yl)-propionic acid with N-bromosuccinimide (NBS) and subsequent dehydrobromination is reported to afford 15% β-(indenon-2-yl)propionic acid and 36% lactone of β-(2-hydroxyindanon-2-yl)propionic acid.[2] It is uncertain whether the latter product results from lactonization of the former product or of an alkylideneindanone derivative or is merely the product of intramolecular displacement of halide from an initial 2-bromoindanone. In this connection, NBS bromination of indanone is reported to be nonspecific, although dehydrobromination of the mixed bromides does constitute a synthesis of indenone.[6]

Finally, two other methods for the preparation of the parent substance which could serve for the synthesis of 2-alkyl derivatives should be noted. The earlier procedure is based on the hydrolysis of the condensation product derived from indene and *p*-nitrosodimethylaniline but suffers from low yield.[7] The second method, which is dependent on pyrolysis of 2-acetoxyindanone, requires special equipment and proceeds in only 8% overall yield from indanone.[6]

These reports suggested that dehydrohalogenation of a 2-alkyl-3-haloindanone might offer the greatest potential for a general 2-alkylindenone synthesis. Accordingly, we have investigated an alternative preparation of the former substances and their dehydrohalogenation to give indenones. In contrast to the previous studies,[2,6] the present approach to the required 3-haloindanones was predicated on an intramolecular Friedel–Crafts acylation of an appropriate β-aryl-β-chloropropionyl chloride **5** (see Scheme I).

SCHEME I



The α-alkyl-β-arylhydracrylic esters (**3**), which generally were prepared in good yield by a Reformatsky condensation of the appropriate benzaldehyde (**1**) and α-bromo ester (**2**), proved to be suitable precursors for this purpose. Alkaline hydrolysis of esters **3** gave the hydracrylic acids **4**. However, α,β-diphenylhydracrylic acid was prepared directly from phenylacetic acid and benzaldehyde by the Ivanov procedure,[8] inasmuch as a Reformatsky condensation of ethyl α-bromophenylacetate with benzaldehyde failed to give the required ester. No effort was made to purify the hydracrylic acids **4** because, with the exception of **4a**, they are known to be diastereomeric mixtures,[5,9] and each diastereomer would serve the present purpose. Treatment of the acids **4** with thionyl chloride in the presence of a catalytic amount of dimethylformamide[10] afforded the requisite β-aryl-β-chloropropionyl chlorides **5**.

Acylation of these substances in methylene chloride was effected with aluminum chloride at 25–40° for 10–180 min; the resulting 3-haloindanones **6** were converted into the desired indenones **7** by treatment with pyridine at 70–90°. In the instance of indenone **7a**, this dehydrohalogenation was effected with collidine in ether at room temperature.[6] The more vigorous conditions failed, apparently as a result of the instability of **7a**. The efficiency of the present indenone synthesis is indicated by the generally good overall yield of **7** and by the fact that intermediates **4**–**6** were utilized without purification. In general, the recorded yields were realized in the initial preparation, and no effort was made to ascertain optimum conditions. Moreover, the present procedure is not restricted to the preparation of 2-alkylindenones, as demonstrated by the preparation of indenone **7a**. However, application of this method to the preparation of 2-phenylindenone from α,β-diphenylhydracrylic acid[8] failed. It may be noted that the conversion of the acid halides **5** into the haloindanones **6** is subject to the usual substituent effects.[11] Thus, halide **5g** afforded 71% 5-methoxyindenone **7g** and 13% 7-methoxyindenone **7h**, after dehydrochlorination of the intermediate 2-alkyl-3-chloroindanones.

Because we required a 5-hydroxyindenone for our concurrent study, the preparation of this system from 5-methoxyindenone **7g** was studied intensively. The results further reflect the susceptibility of the indenone system to electrophilic[6] and nucleophilic[1] attack. Thus, ether cleavage of **7g** with aluminum chloride in toluene is accompanied by alkylation of the solvent to furnish indanone **12**, characterized as an aryloxyacetic acid. This result illustrates the susceptibility of the indenone system to attack by the electrophilic aluminum chloride, yielding carbonium ion **10** which alkylates the solvent (see Scheme II). Attempted ether cleavage of **7g** by sodium iodide–hydrogen bromide in acetic acid gave 2-ethyl-5-hydroxyindanone (**11**) presumably by reduction of the 3-iodo compound. This result is indicative of the sensitivity of the indenone system to nucleophilic attack. The latter property is also evident in the alkylation of hydroxyindenone **8** (prepared as described below) with chloroacetic acid; the only isolable product was the dimeric substance **9**.

Finally, treatment of 2-butylindenone (**7e**) with dimethylamine gave 73% indanone **13**. The hydrochloride of **13** has properties in excellent accord with those reported for that derived by reaction of dimethyl-

(6) C. S. Marvel and C. W. Hinman, *J. Amer. Chem. Soc.*, **76**, 5435 (1954).

(7) R. Stoermer and E. Asbrand, *Chem. Ber.*, **64**, 2796 (1931).

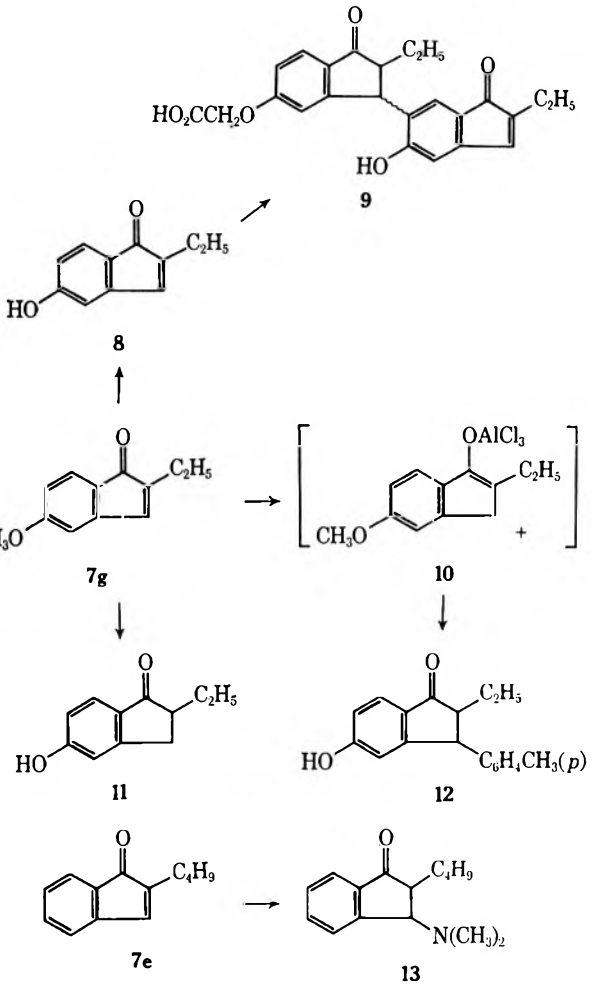
(8) (a) D. Ivanov and N. Nicoloff, *Bull. Soc. Chim.*, **51**, 1325 (1932); (b) H. E. Zimmerman and M. D. Traxler, *J. Amer. Chem. Soc.*, **79**, 1920 (1957).

(9) L. Canonica and F. Pelizzoni, *Gazz. Chim. Ital.*, **84**, 553 (1954); *Chem. Abstr.*, **50**, 879g (1956).

(10) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

(11) (a) W. S. Johnson, *Org. React.*, **2**, 125 (1944); (b) V. Askam and W. H. Linnell, *J. Chem. Soc.*, 2435 (1954).

SCHEME II

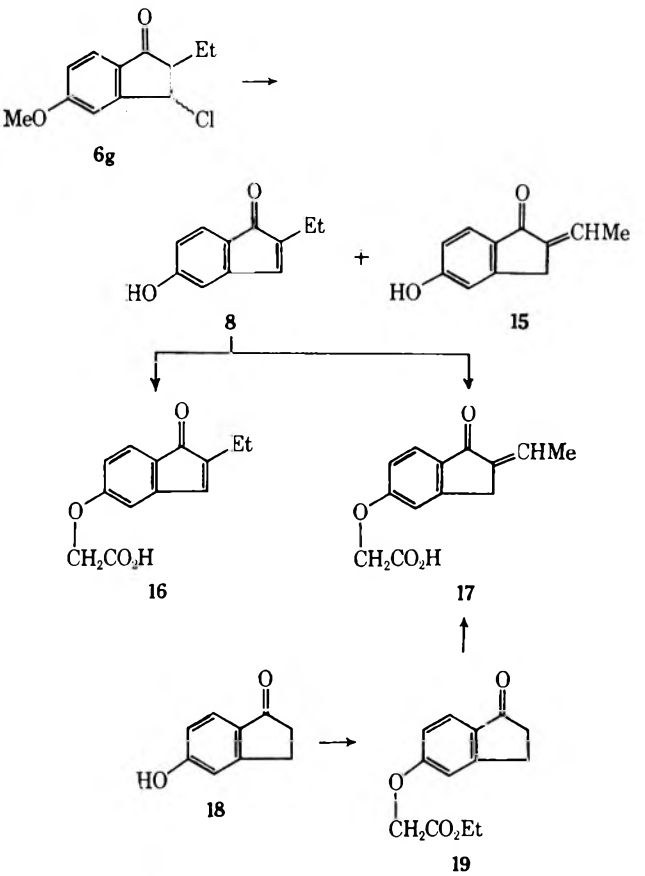


amine with 2-bromo-2-butylindanone.[1a] These results suggest that the latter preparation of **13** indeed proceeds *via* an indenone intermediate and that the dehydrobromination of 2-alkyl-2-bromoindanones may constitute a 2-alkylindenone synthesis of greater potential than indicated by the work of House and his coworkers.[2]

Normal formation of carbonyl derivatives was observed, but in the instance of indenone **7a**, unusual reactivity of the derivative was noted. On reaction with semicarbazide hydrochloride, **7a** furnished a product possessing a melting point of 236–245° in reasonable agreement with the recorded.[7] However, recrystallization of this material from dilute methanol was accompanied by a sharp drop in the melting point to 208–212°. Consideration of the combustion analysis and the mass spectrum of the resulting material indicated it to be a mixture of the semicarbazones of **7a** and 3-methoxyindanone. In particular, the mass spectrum was characterized by ions at *m/e* 219 and 187; however, the absence of a metastable ion for the 219 to 187 transition suggested that the *m/e* 187 ion was a molecular ion. Indeed, tlc of this material indicated it to be a mixture of two substances; however, the limited solubility of these materials precluded their separation by chromatographic techniques. This result is unique in that it represents an example of the Michael addition of a nucleophile to a ketonic derivative of an α,β-unsaturated ketone.

Finally, we would indicate two instances of the isomerization of an alkylindenone into an alkylideneindanone. These isomerizations are noteworthy because House and his collaborators[2] failed to effect detectable isomerization of 2-ethylindenone into 2-ethylideneindanone with γ-collidine at 175°. The first such isomerization was encountered in the preparation of 2-ethyl-5-hydroxyindenone (**8**), which eventually was effected by the action of aluminum chloride on 2-ethyl-5-methoxyindenone (**7g**) or 3-chloro-2-ethyl-5-methoxyindanone (**6g**) in tetrachloroethane. This synthesis of **8** also afforded 2% ethylidene derivative **15** (see Scheme III). Treatment of the sodium salt of **8** with

SCHEME III



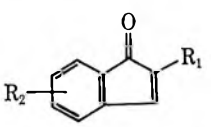
sodium bromoacetate in diglyme results in a similar isomerization. The alkylated material, which was isolated in low yield, consisted of an approximately 13:1 mixture of the ethylindenone **16** and the ethylideneindanone **17**. The latter substance was identical with that prepared independently from 5-hydroxyindanone (**18**). Alkylation of **18** with ethyl chloroacetate gave the oxyacetic ester **19**, which on treatment with base and acetaldehyde afforded the ethylidene derivative **17**.

Physical Properties.—As noted previously,[2,6] the infrared spectra of the various indenones **7** are characterized by sharp carbonyl stretching bands at approximately 5.85 μ and C=C stretching bands at 6.25 μ. The ultraviolet spectrum of indenone (**7a**) is characterized by intense absorption maxima at 233 and 238 mμ in addition to the long wavelength (318 mμ) maximum previously reported (see Table I).[6] A 2-alkyl substituent results in a bathochromic shift of 2–5 mμ in the short wavelength maxima. Further substitution

by a 6-alkyl group causes an additional bathochromic shift in these maxima. The position and intensity of the 318-mμ maximum in the spectrum of **7a** is largely unaffected by alkyl groups in the 2 and 6 positions. In the instance of the 5-oxygenated indenones **7g–i** and **8**, resonance interaction of the 5 substituent with the carbonyl group causes a bathochromic shift of each maximum and a coalescence of the two lower maxima. In the absence of an oxygen function at C-6, the intensity of the short wavelength maximum is diminished and that of the longer absorption is enhanced. However, the presence of an additional methoxy group at C-6 largely negates these effects on the extinction coefficients. A 7-methoxy substituent causes a red shift of 47 mμ in the long wavelength absorption, but the position of the short maximum is unaffected, although a coalescence of the two maxima of the parent substance is observed. The effect of this substituent on the extinction coefficients parallels that of a 5-methoxy group.

TABLE I

ULTRAVIOLET SPECTRA OF INDENONE AND SUBSTITUTED INDENONES



Compd	R_1	R_2	λ_{max}, mμ (ε)		
7a	H	H	233 (36900)	238 (37400)	318 (1820)
7b	Me	H	238 (38600)	243 (43600)	317 (1370)
7c	Et	H	235 (40000)	242 (46100)	318 (1270)
7d	*i*-Pr	H	236 (40600)	242 (47100)	318 (1200)
7e	Bu	H	235 (39100)	241 (42800)	320 (1120)
7f	Et	6-*i*-Pr	240 (38400)	245 (41600)	316 (4100)
7g	Et	5-MeO	218 (12800)	260 (30500)	332 (3950)
8	Et	5-HO	218 (11300)	260 (26300)	333 (3300)
7i	Me	5,6-MeO		261 (38600)	330 (2040)
7h	Et	7-MeO	235 (32400)		365 (4140)

The nmr spectrum of indenone (**7a**) shows two single-proton doublets (J = 5.5 Hz) at δ 7.52 and 5.83, which are ascribed to C-3 and C-2, respectively. The C-3 resonance of the 5- and 7-methoxy derivatives of 2-ethylindenone is apparent at δ 6.90. This resonance appears as a sharp triplet (J = 2.0 Hz) in the spectrum of the latter substance as a result of allylic coupling with the methylene portion of the alkyl substituent. Comparison of the C-3 resonance with that seen in the spectrum of the 5-methoxy derivative suggests that the C-3 proton may also be subject to long range coupling with C-7 ($J_{3,7} \cong 1$ Hz). However, this coupling is only weakly evident in the spectrum of 5,6-dimethoxy-2-methylindenone (**7i**). The spectra of the remaining indenones are not particularly informative because the C-3 resonance is obscured by the aryl proton resonances.

Experimental Section

General.—All melting points and boiling points are uncorrected. The melting points were determined in open capillary tubes on a Mel-Temp apparatus. In the instance of that compound melting below ambient temperature, a vessel containing a sample of the substance was inserted in a cooling bath; the temperature of the bath was allowed to equilibrate with ambient temperature, and the melting range of the substance was recorded by a thermometer immersed in the sample. Infrared spectra were determined in pressed KBr disks on a Perkin-Elmer Model 21 spectrophotometer, and the ultraviolet spectra were measured in methanol solution with a Cary Model 11 recording spectrophotometer. Nmr spectra were determined in deuteriochloroform, except where noted otherwise, on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectrum was determined on a AEI MS-9 spectrometer. All evaporations were carried out at reduced pressure. The petroleum ether used was that fraction boiling at 30–60°.

Preparation of the Ethyl α-Alkyl-β-arylhydracrylates (3).—The general procedure described previously[12] was used for the preparation of these esters, the characterization of which is given in Table II. In one experiment, attempted distillation of crude ethyl β-(3,4-dimethoxyphenyl)-α-methylhydracrylate (**3h**) gave **ethyl 3,4-dimethoxy-α-methylcinnamate** (50%): bp 165–167° (0.85 mm); n^{25}D 1.5637; uv max 231, 290, 308 mμ (ε 14,800, 16,200, 15,700); ir 5.85, 6.12, 6.23, 8.02 μ.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.86; H, 7.14.

In a second experiment the crude ester obtained by removal of the extraction solvent partially crystallized. This mixture was triturated with ether and filtered to give white crystals of **ethyl β-(3,4-dimethoxyphenyl)-α-methylhydracrylate (3h)**. This material was recrystallized from ether–petroleum ether to give white crystals, mp 95–97°. This substance most likely is a pure diastereomer and its characterization is given in Table II. For the preparation of indenone **7i**, the crude diastereomeric mixture was used. The absence of cinnamate esters in the products of Table I was indicated by their ir (no strong absorption at 6.24 μ) and uv spectra.

Preparation of the Indenones (7).—The following experiments illustrate the general procedure. A solution of 12.6 g (50.0 mmol) of ethyl α-ethyl-β-(3-methoxyphenyl)hydracrylate (**3g**) and 8.42 g (150 mmol) of potassium hydroxide in 140 ml of methanol and 20 ml of water was allowed to stand at room temperature for 16 hr. The bulk of the solvent was evaporated, and the resulting white mass was treated successively with 100 ml of water, 50 ml of cracked ice, 120 ml of 10:1 ether–hexane, and 60 ml of 4 *N* HCl. The phases were separated, and the aqueous phase was extracted with additional ether. The combined organic extracts were washed with water, dried, and evaporated at room temperature to give 11.3 g (100%) of α-ethyl-β-(3-methoxyphenyl)hydracrylic acid as a colorless syrup. This mixture of diastereoisomers was used for the subsequent stages without attempted purification; the ir and uv spectra of this product indicated no formation of the corresponding cinnamic acid.

A stirred solution of 12.5 ml (20.6 g, 0.173 mol) of thionyl chloride and 0.15 g (2.0 mmol) of dimethylformamide in 40 ml of methylene chloride was added to a solution of 16.14 g (0.072 mol) of the above hydracrylic acid in 60 ml of methylene chloride over 30 min. The reaction mixture was stirred an additional 30 min at room temperature and then heated at reflux for 15 min. Evaporation at room temperature gave crude β-chloro-α-ethyl-β-(3-methoxyphenyl)propionyl chloride. In the absence of dimethylformamide catalysis, the acid derived from ester **3d** was only partially converted into the corresponding β-chloropropionyl chloride.

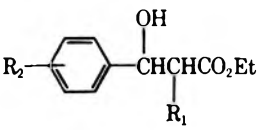
In a pilot experiment the above acid chloride was converted into an amide by treating an ether solution of the compound with anhydrous ammonia at 0° for 1 min. After treatment with water and washing with saturated $NaHCO_3$, the ether solution was dried and evaporated. The crude chloroamide was recrystallized from hexane–ethyl acetate giving white needles: mp 130–132°; uv max 278 mμ (ε 2200); ir 2.98, 3.15, 3.42, 6.04, 6.25 μ.

Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.62; H, 6.67; Cl, 14.67; N, 5.80. Found: C, 59.36; H, 6.79; Cl, 14.57; N, 5.87.

To a stirred solution of the above β-chloro acid chloride in 150 ml of methylene chloride was added 19.3 g (0.080 mol) of anhydrous aluminum chloride powder at room temperature. After the vigorous initial reaction had subsided the dark brown solution was allowed to stand at room temperature for 10 min. The reaction mixture was treated with ice, and the product was extracted with ether. The extract was washed with water and saturated $NaHCO_3$, dried, and evaporated. The resulting crude 3-chloro-2-ethyl-5-methoxyindanone (13.68 g; λ_{max} 266, 287 mμ; precipitate with alcoholic silver nitrate) was dissolved in 50 ml of pyridine and stirred at 70° for 30 min. Treatment of the cooled reaction mixture with ether gave a precipitate. The mix-

(12) R. L. Shriner, *Org. React.*, **1**, 1 (1942).

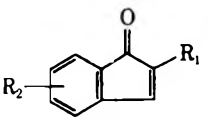
TABLE II
ETHYL α-ALKYL-β-ARYLHYDRACRYLATES



Compd	R_1	R_2	Yield, %	Bp (mm), °C	$n^{25}D$	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
3a	H	H	90	99 (0.15)[a]	1.5085	$C_{11}H_{14}O_3$	68.02	7.27	67.89	7.22
3b	Me	H	75	109–110 (0.50)[b]	1.5007	$C_{12}H_{16}O_3$	69.21	7.74	69.09	7.50
3c	Et	H	66	120–122 (0.20)[c]	1.4991[c]	$C_{13}H_{18}O_3$	70.24	8.16	70.45	8.11
3d	*i*-Pr	H	70	110 (0.15)[d]	1.4996	$C_{14}H_{20}O_3$	71.16	8.53	70.95	8.33
3e	Bu	H	79	122 (0.25)	1.4914	$C_{15}H_{22}O_3$	71.97	8.86	71.87	8.74
3f	Et	4-*i*-Pr	65	127–128 (0.55)	1.4964	$C_{16}H_{24}O_3$	72.69	9.15	72.57	9.00
3g	Et	3-MeO	66	148–150 (0.35)	1.5060	$C_{14}H_{20}O_4$	66.64	7.99	66.64	7.93
3h	Me	3,4-MeO	30	Mp 95–97		$C_{14}H_{20}O_5$	62.67	7.51	62.86	7.40

[a] Described previously without characterization by V. N. Andrievskii, *J. Russ. Phys. Chem. Soc.*, **40**, 1635 (1908). [b] Described without characterization by G. Dain, *ibid.*, **28**, 593 (1896). [c] Lit.[9] bp 143–144° (3 mm), $n^{25}D$ 1.525. [d] Lit.[9] bp 132° (3 mm).

TABLE III
INDENONES



Compd	R_1	R_2	Yield, %[a]	Recrystn solvent	Bp (mm), °C	Mp, °C	$n^{25}D$	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
7a	H	H	49		75–77 (1.5)[b]		1.5985[b]	C_9H_6O	83.10	4.66	82.87	4.75
7b	Me	H	71	Ether–pet ether		45–47[c]		$C_{10}H_8O$	83.31	5.59	82.99	5.56
7c	Et	H	53		74.5–75.0 (0.25)[d]	9–10	1.5716	$C_{11}H_{10}O$	83.51	6.37	83.15	6.37
7d	*i*-Pr	H	62		84–86 (1.10)		1.5582	$C_{12}H_{12}O$[e]				
7e	Bu	H	81	Pet ether	96–100 (0.65)	35–36		$C_{13}H_{14}O$	83.83	7.58	83.83	7.51
7f	Et	6-*i*-Pr	69		96–99 (0.15)		1.5522	$C_{14}G_{16}O$	83.96	8.05	84.11	8.03
7g	Et	5-MeO	71	Pet ether		37–38		$C_{12}H_{12}O_2$	76.57	6.43	76.35	6.39
7h	Et	7-MeO	13	Pet ether		46–47		$C_{12}H_{12}O_2$	76.57	6.43	76.36	6.44
7i	Me	5,6-MeO	46	Ether–pet ether		84–85[f]		$C_{12}H_{12}O_3$	70.57	5.92	70.36	5.85

[a] Based on material of analytical purity obtained from the corresponding ethyl β-aryl-α-substitued hydracrylate (Table II). [b] Lit.[6] bp 61–63° (0.9 mm), $n^{20}D$ 1.5981; lit.[7] bp 69–70° (0.35 mm). [c] Lit.[3a] mp 47.0–47.5°. [d] H. O. House and D. J. Reif, *J. Amer. Chem. Soc.*, **79**, 6491 (1957), bp 140–150° (10 mm). [e] Satisfactory combustion analyses were unobtainable because of instability and so the physical constants may be in doubt. See Table IV for characterization as the semicarbazone. [f] Lit.[1a] mp 85–86°.

ture was treated with 2 *N* HCl and the organic phase was washed successively with water, saturated $NaHCO_3$, and water. The ether solution was dried and evaporated to give 11.52 g (85%) of a mixture of **2-ethyl-5-methoxyindenone** (**7g**) and **2-ethyl-7-methoxyindenone** (**7h**). These substances could not be separated by distillation under reduced pressure.

A 1-g sample was subjected to column chromatography on diatomaceous silica using the system heptane–methoxyethanol (1:1).[13] The fraction eluted at peak hold-back volume 2.5 (Vm/Vs = 1.83) was evaporated to give 833 mg of **2-ethyl-5-methoxyindenone** (**7g**) as yellow crystals. The fraction eluted at peak hold-back volume 3.1 was evaporated to give 152 mg of **2-ethyl-7-methoxyindenone** (**7h**) as yellow crystals. The characterization of these substances is given in Table III.

Since the above experiments demonstrated the feasibility of the present synthetic approach for the preparation of indenones, the intermediates required for the preparation of **7a–f** and **7i** were not purified prior to their further use.

2-Ethyl-5-hydroxy-3-*p*-tolylindan-1-one (**12**).—To a stirred solution of β-chloro-α-ethyl-β-(3-methoxyphenyl)propionyl chloride [prepared by the above procedure from 6.77 g (30 mmol) of hydracrylic acid **4g**] in 60 ml of dry methylene chloride at 0° was added 10 g (75 mmol) of aluminum chloride over 1 min. Following the addition, the reaction mixture was stirred for 15 min. The solvent was evaporated at room temperature, and the resulting red residue was treated with 75 ml of toluene. The mixture was refluxed with stirring for 3 min and poured onto 300 ml of cracked ice. The product was extracted with ether, and the extract was washed successively with 2 *N* HCl and water. Acidic material was extracted into 1.2 *N* NaOH and retrieved by acidification with 4 *N* HCl and ether extraction. The extract was washed with water, dried, and evaporated to give a gum which crystallized on hexane trituration. Recrystallization from isopropyl alcohol–hexane gave 1.75 g of white crystals: mp 146–148°; concentration of the mother liquor and further crystallization gave a total yield of 2.60 g (31%); uv max 222, 271, 297 (sh) mμ (ε 16,900, 11,100, 8500); ir 3.08, 3.38, 5.95, 6.29 μ. An aryloxyacetic acid derivative was prepared and recrystallized from acetone–hexane: mp 161.5–163°; uv max 220, 268, 295 mμ (ε 22,500, 14,900, 9600); ir 5.75, 5.87 μ; nmr δ 7.70 (d, 1, *J* = 7.0 Hz, C-7), 7.14 (s, 4, H of *p*-tolyl ring), 7.08 (m, 1, C-6), 6.61 (broad s, 1, C-4), 4.73 (s, 2, $-OCH_2-$), 4.20 (d, 1, *J* = 5.0 Hz, C-3), 2.50 (m, 1, C-2), 2.26 (s, 3, aryl CH_3), 1.70 (m, 2, 2, CH_2CH_3), 1.17 (t, 3, *J* = 7.0 Hz, CH_2CH_3).

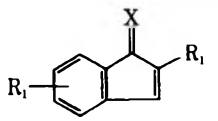
Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.15; H, 6.26.

Reaction of 2-Ethyl-5-methoxyindenone (**7g**) **with Sodium Iodide–Hydrogen Bromide in Acetic Acid.**—A mixture of 0.47 g (2.5 mmol) of 2-ethyl-5-methoxyindenone (**7g**) and 1.50 g (10 mmol) of sodium iodide in 10 ml of 15% HBr in acetic acid was heated at reflux for 17 hr under argon. The dark reaction mixture was treated with water and extracted with ether. The extract was washed successively with water, 10% sodium thiosulfate solution, and water. The aqueous phase from a partition of the extract with 1.2 *N* NaOH was acidified with 4 *N* HCl and extracted with ether. The washed and dried extract was evaporated to give 0.25 g of crude phenolic material. Crystallization from benzene–hexane gave 107 mg (24%) of yellow-brown crys-

(13) For a complete description of this technique as developed by Mr. C. Pidacks of these laboratories, see 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).

TABLE IV

INDENONE DERIVATIVES



Indenone	R_1	R_2	X[a]	Mp, °C[b]	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7b	Me	H	S	189–191[c]	$C_{11}H_{11}N_3O$	65.67	5.51	20.88	65.65	5.79	20.53
7c	Et	H	S	183–185[d]	$C_{12}H_{13}N_3O$	66.95	6.09	19.52	66.97	6.11	19.80
7c	Et	H	DNP	247–248 dec[e,f]							
7d	*i*-Pr	H	S	171–173	$C_{13}H_{15}N_3O$	68.10	6.59	18 33	68.11	6.56	18.26
7e	Bu	H	S	134–136	$C_{14}H_{17}N_3O$	69.11	7.04	17.27	68.70	6.97	17.27
7f	Et	6-*i*-Pr	S	173–175	$C_{15}H_{19}N_3O$	70.00	7.74	16.63	69.88	7.53	16.39
7g	Et	5-MeO	S	162–164	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.64	6.49	16.84
7h	Et	7-MeO	S	171–173	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.32	6.13	17.05
7i	Me	5,6-MeO	S	209–211	$C_{13}H_{15}N_3O_3$	59.76	5.79	16.01	60.03	5.83	16.01
7i	Me	5,6-MeO	O	157–159[g]	$C_{12}H_{13}NO_3$			6.39			6.28

[a] S = semicarbazone; DNP = 2,4-dinitrophenylhydrazone; O = oxime. [b] All compound were recrystallized from dilute methanol unless specified otherwise. [c] Lit.[3a] mp 192–193°. [d] Lit.[3a] mp 181°. [e] From acetic acid. [f] H. O. House and D. J. Reif, *J. Amer. Chem. Soc.*, 79, 6491 (1957), mp 247–248°. [g] Lit.[5] mp 165°.

tals, mp 142–144°. An analytical sample of **2-ethyl-5-hydroxy-1-indanone** was obtained by sublimation at 0.01 mm (bath, 130°): mp 143–145°; uv max 224, 269, 290, 296 mμ (ε 11,300, 10,900, 9350, 9350); ir 2.45, 3.18, 5.98, 6.20, 6.27 μ; nmr (DMSO-d_6) δ 7.51 (d, 1, J = 10 Hz, C-7), 6.90 (s, 1, C-4), 6.84 (m, 1, C-6), 3.04 (d, 1, J = 8 Hz, C-3), 2.78 (d, 1, J = 4 Hz, C-3), 2.50 (m, 1, C-2), 1.67 (m, 2, CH_2), 0.88 (t, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.98; H, 7.15.

Reaction of 2-Ethyl-5-hydroxyindenone with Chloroacetic Acid.—A solution of 2.8 g (16 mmol) of 2-ethyl-5-hydroxyindenone, 1.7 g (18 mmol) of chloroacetic acid, and 1.4 g (35 mmol) of sodium hydroxide in 50 ml of water was heated at *ca.* 100° for 6 hr. During the reaction 0.3 g (3 mmol) of additional chloroacetic acid and 1.5 ml of 2.5 *N* NaOH were added. The reaction mixture was cooled, treated with 15 ml of 4 *N* HCl, and extracted with ether. The extract was washed with water, dried, and evaporated. The red residue was chromatographed on a column of silica gel. Elution with benzene progressively enriched in ether gave impure starting material, (*ca.* 50%) followed by a yellow solid (350 mg) which was recrystallized from acetone–hexane to give **[2-ethyl-3-(2-ethyl-5-hydroxy-1-oxo-6-indenyl)-1-(oxo-5-indenyl)-1-oxo-5-indanyloxy]acetic acid** (9) as an orange powder: mp 142–147°; uv max 222, 265, 295 (sh), 335 mμ (ε 20,300, 40,000, 9100, 2400); ir 2.96, 3.40, 5.75, 6.19 μ; nmr (DMSO-d_6) δ 7.64 (d, 1, J = 8 Hz, C-7), 7.20 (s, 1, C-3′), 7.02 (q, 1, J = 2 and 8 Hz, C-6), 6.97 (s, 1, C-7′), 6.66 (broad s, 2, C-4 and C-4′), 4.73 (s, 2, OCH_2CO), 4.44 (d, 1, J = 4 Hz, C-3), 2.50 (m, 1, C-2), 2.16 (q, 2, J = 7 Hz, CH_2CH_3′), 2.08 (s, 6, acetone), 1.73 (m, 2, CH_2CH_3), 1.10 (t, 3, J = 7 Hz, CH_2CH_3′), 0.97 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{24}H_{22}O_6 \cdot C_3H_6O$: C, 69.81; H, 6.08. Found: 69.80; H, 6.24.

2-Butyl-3-dimethylaminoindanone (13) Hydrochloride.—A solution of 2.05 g (11 mmol) of 2-butylindenone (**7e**) in 100 ml of ethanol that had been saturated with dimethylamine at 0° was heated at reflux for 18 hr. The solvent was removed, and the residue was distributed between ether and 2 *N* hydrochloric acid. The acid solution was chilled and rendered alkaline by addition of KOH pellets. The resulting mixture was extracted with ether, and the dried solution was evaporated to give 1.82 g of liquid. This material was dissolved in ether, and a solution of hydrogen chloride in isopropyl alcohol was added dropwise until precipitation ceased; filtration gave 1.93 g (65%) of the **hydrochloride of 13**: white crystals, mp 140–141° (lit.[1a] mp 136–138°) (recrystallization from isopropyl alcohol–ether failed to alter the melting point); uv max 206, 242, 289 mμ (ε 29,200, 13,000, 1210); ir 3.90, 4.15, 5.80, 6.19, 6.24 μ; nmr δ 13.0 (broad, 1, N^+H), 8.60 (m, 1, C-7), 7.80 (m, 3, aryl H), 5.06 (d, 1, C-3), 3.26 (m, C-2), 2.87 [broad s, $N(CH_3)_2$].

Anal. Calcd for $C_{15}H_{21}NO \cdot HCl$: C, 67.27; H, 8.28; Cl, 13.23; N, 5.23. Found: C, 66.90; H, 8.29; Cl, 13.04; N, 5.19.

Semicarbazones.—These derivatives were prepared by the usual technique[14] and their characterization is given in Table IV. The uv spectra of the semicarbazones of **7b–f** were characterized by maxima at 235–240 mμ (ε 16,600–18,600), 250–252 (14,200–15,800), 288–290 (13,600–14,800), 316–317 (12,800–14,000), and 323–325 (11,700–12,600); for semicarbazone of **7g** uv max 245 mμ (ε 17,600), 290 (18,880), 332 (15,900); for semicarbazone of **7h** uv max 207 mμ (ε 29,000), 239 (15,200), 288 (sh) (15,900), 291 (16,200), 345 (9580); for semicarbazone of **7i** uv max 255 mμ (ε 19,600), 296 (26,400), 328 (14,400), 338 (12,900).

In the instance of indenone **7a**, 500 mg of the ketone gave 470 mg (65%) of yellow crystals: mp 236–245° dec (lit.[7] 240–250° dec) (on recrystallization of the solid from dilute methanol, the melting point dropped to 208–212° dec); mass spectrum (70 eV) *m/e* 219, 204, 187, 161, 145, 144, 120, 115, 90; nmr (DMSO-d_6) δ 10.8 (s, 1, NH), 9.50 (s, 1, NH), 8.0–7.0 (m, 10), 6.85 (broad s, 2, NH_2), 6.54 (broad s, 2, NH_2), 4.96 (m, 1, X H of ABX system), 3.33 (s, 3, OCH_3), 3.00, 2.85 (m, 2, AB H's of ABX system).

Anal. Calcd for $(C_{10}H_9N_3O)_2 \cdot CH_3OH$: C, 62.05; H, 5.46; N, 20.68. Found: C, 62.10; H, 5.50; N, 20.56.

2-Ethyl-5-hydroxyindenone (8).—To a solution of crude 3-chloro-2-ethyl-5-methoxyindan-1-one (18.8 g, 84 mmol) in 250 cc of tetrachloroethane was added 26.7 g (200 mmol) of powdered aluminum chloride over 3 min with stirring. The resulting mixture was stirred and heated at 110° for 20 min and poured onto 300 g of ice and 60 cc of concentrated HCl. The product was extracted with ether, and the extract was washed with half-saturated NaCl. Acidic material was extracted into 0.5 *N* NaOH and recovered by acidification with 4 *N* HCl and ether extraction. The extract was washed with water, dried, and evaporated. The resulting semicrystalline product was chromatographed on 250 g of silica gel and eluted with benzene successively enriched in ether. The total yield of crude product obtained in this way was 87%.

An analytical sample was prepared by column chromatography on diatomaceous silica using a heptane–ethyl acetate–methanol–water (70:30:15:6) system. The fraction eluted at peak hold-back volume 1.1 (Vm/Vs = 2.65) was recrystallized from acetone–hexane to give orange crystals: mp 155–156.5°; uv max 218, 260, 333 mμ (ε 11,300, 26,300, 3300); ir 3.04, 5.92, 6.24 μ; nmr ($CDCl_3$–DMSO-d_6) δ 8.90 (broad s, 1, OH), 7.16 (q, 1, J = 2 and 6 Hz, C-7), 6.91 (broad s, 1, C-3), 6.49 (d, 1, J = 2 Hz, C-4), 6.46 (q, 1, J = 2 and 6 Hz, C-6), 2.24 (q, 2, J = 7 Hz, CH_2), 1.10 (t, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.51; H, 5.86.

The fraction eluted at peak hold-back volume 3.9 yielded **2-ethylidine-5-hydroxyindan-1-one** (15) as off-white crystals on evaporation and recrystallization from acetone–hexane: mp

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 1000.

219–222°; uv max 245, 265, 290, 315 mμ (ε 10,100, 10,100, 12,000 16,000); ir 2.93, 3.25, 5.93, 6.10, 6.23, 6.35 μ; nmr (DMSO-d_6) 7.57 (d, 1, J = 8 Hz, C-7), 6.89 (d, 1, J = 2 Hz, C-4), 6.85 (q, 1, J = 2 and 8 Hz, C-6), 6.63 (q, 1, J = 7 Hz, CH_3CH), 3.56 (broad s, 2, CH_2), 1.90 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.96; H, 6.07.

Similar treatment of indenone methyl ether **7g** afforded crude **8** from which **15** was isolated as above in low yield.

Alkylation of 2-Ethyl-5-hydroxyindenone (8) with Bromoacetic Acid.—Sodium bromoacetate was prepared by treating 1.39 g (10.0 mmol) of bromoacetic acid with 4 ml of 2.5 *M* sodium hydroxide and removing the solvent. The sodium salt of 2-ethyl-5-hydroxyindenone (**8**) was prepared similarly from 0.88 g (5.0 mmol) of **8** and 2 ml of 2.5 *M* sodium hydroxide. A solution of the sodium phenolate in 30 ml of diglyme was added over 2 hr to a stirred and heated (steam bath) suspension of the sodium bromoacetate in 30 ml of diglyme. The mixture was allowed to stand at room temperature for approximately 16 hr and was then heated at 130° for 15 min. The cooled mixture was treated with 40 ml of saturated sodium bicarbonate solution and extracted with three 40-ml portions of ether. The aqueous phase was acidified with 4 *N* HCl and extracted with ether. These ethereal extracts were washed with saline, dried, and evaporated. Evaporation (final pressure ~0.5 mm) gave 700 mg of yellow crystals. This material was recrystallized from methanol to give 113 mg (10%) of **(2-ethylindenon-5-yl)oxyacetic acid (16)** as yellow crystals, mp 164–166°. An additional recrystallization from methanol gave yellow crystals: mp 167–169°; uv max 218, 258, 300 mμ (ε 8700, 22,600, 2400); ir 3.43, 5.75, 5.87, 6.18 μ; (DMSO-d_6) δ 7.27 (d, 1, J = 8 Hz, C-7), 7.21 (s, 1, C-3), 6.73 (d, 1, J = 2 Hz, C-4), 6.59 (q, 1, $J_{4,6}$ = 2 Hz, $J_{6,7}$ = 8 Hz, C-6), 4.72 (s, 2, OCH_2), 2.20 (q, 2, J = 7 Hz, CH_2CH_3), 1.08 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.13; H, 5.42.

The combined methanol filtrates were concentrated and cooled to give 125 mg of solid, mp 158–163°. Tlc in an ethyl acetate–heptane–acetic acid (50:5:2) system revealed two substances. This material was subjected to column chromatography on diatomaceous silica using a heptane–methanol system. The fraction eluted at peak hold-back volume 9.5 (Vm/Vs = 2.48)was evaporated to give 33 mg (13% total) of **16**, mp 169–171°.

The fraction eluted at peak hold-back volume **15** was evaporated to give a residue that was recrystallized from methanol to give 20 mg (1%) of **(2-ethylideneindanon-5-yl)oxyacetic acid (17)** as white crystals, mp 179–182°. This material was identical in all respects with that described below.

Ethyl (Indanon-5-yl)oxyacetate (19).[15]—To a stirred, ice-cooled solution of 20.0 g (0.135 mol) of 5-hydroxyindanone (**18**)[16] in 65 ml of dimethylformamide was added in small increments 6.40 g (0.16 mol) of a 60.2% sodium hydride in mineral oil dispersion; stirring was continued for 60 min after completion of the addition. Ethyl chloroacetate (18.4 g, 0.15 mol) was added, and stirring was continued for 2 hr. The solution was poured into ice water and extracted with ether. The dried solution was evaporated to give an oil that was triturated with heptane. The resulting solid was crystallized from ethyl acetate–heptane to give 13.50 g (43%) of crystals: mp 61.5–63.0°; uv max 221, 264, 287, 293 mμ (ε 14,600, 14,500, 9150, 8800); ir 5.71, 5.88, 6.19, 6.28 μ.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.94; H, 6.28.

(2-Ethylideneindanon-5-yl)oxyacetic Acid (17).—A solution of 9.00 g (39.6 mmol) of ethyl (indanon-5-yl)oxyacetate (**19**) and 2.16 g (40.5 mmol) of sodium methoxide in 60 ml of methanol was stirred for 10 min, at which time a solid separated. A solution of 3.10 g (70 mmol) of acetaldehyde in 5 ml of methanol was added dropwise, and the mixture was stirred at ambient temperature for 1 hr and then poured into water. The aqueous solution was extracted with ether and then acidified with HCl. This solution was extracted with ether, and the dried extracts were evaporated to give a solid that was recrystallized from methanol to give 3.50 g (39%) of solid, mp 182–184°. The sample was further purified by partition with ether and saturated $NaHCO_3$, evaporation of the ether phase, and recrystallization from methanol: mp 179–182°; uv max 238, 285, 308 mμ (ε 9300, 16,600, 17,700); ir 3.50, 4.00, 5.73, 5.92, 6.15, 6.26 μ; nmr (DMSO-d_6) δ 7.66 (d, 1, J = 9 Hz, C-7), 7.08 (d, 1, J = 2 Hz, C-4), 7.00 (dd, 1, $J_{4,6}$ = 2 Hz, $J_{6,7}$ = 9 Hz, C-6), 6.70 (q, 1, J = 7 Hz, CH_3CH), 4.82 (s, 2, OCH_2), 3.58 (s, 2, 3-CH_2), 1.86 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.91; H, 5.40.

Registry No.—**3a**, 5764-85-2; **3b**, 24744-96-5; **3c**, 24744-97-6; **3d**, 24744-98-7; **3e**, 24744-99-8; **3f**, 24745-00-4; **3g**, 24745-01-5; **3h**, 24745-02-6; **7a**, 480-90-0; **7b**, 5728-95-0; semicarbazone of **7b**, 24741-67-1; **7c**, 24741-68-2; semicarbazone of **7c**, 24741-69-3; **7d**, 24799-55-1; semicarbazone of **7d**, 24741-70-6; **7e**, 24741-71-7; semicarbazone of **7e**, 24741-72-8; **7f**, 24741-73-9; semicarbazone of **7f**, 24741-74-0; **7g**, 24741-75-1; semicarbazone of **7g**, 24741-76-2; **7h**, 24741-77-3; semicarbazone of **7h**, 24741-78-4; **7i**, 4900-43-0; semicarbazone of **7i**, 24741-80-8; oxime of **7i**, 4900-48-5; **8**, 24741-82-0; **9**, 24741-83-1; **12**, 24741-84-2; hydrochloride of **13**, 24741-85-3; **15**, 24741-86-4; **16**, 24741-87-5; **17**, 24741-88-6; **19**, 24741-89-7; ethyl 3,4-dimethoxy-α-methylcinnamate, 5415-49-6; 2-ethyl-5-hydroxy-1-indanone, 24741-91-1; aryloxyacetic acid derivative of **12**, 24766-63-0.

Acknowledgment.—We are indebted to Messrs. L. M. Brancone, W. Fulmor, and C. Pidacks, and their associates for the microanalyses, spectral data, and liquid-liquid partition column chromatography, respectively.

(15) This experiment was performed by Dr. R. M. Sheeley.

(16) W. A. Johnson, J. M. Anderson, and W. E. Shelberg, *J. Amer. Chem. Soc.*, **66**, 218 (1944), and references cited therein.

Stereochemistry of Hydroboration of Methylenecyclohexanes

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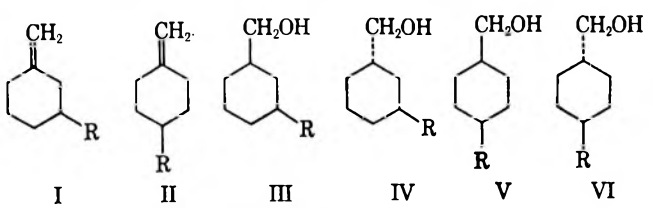
Hydroboration of 3- and 4-methyl- and 3- and 4-*t*-butylmethylenecyclohexanes yielded, after oxidation, predominantly the axial–equatorial disubstituted cyclohexanes. Similar results were obtained when dichloroborane was used as the hydroborating agent. Dicyclohexylborane gave equal amounts of axial and equatorial products.

The addition of nucleophiles to unhindered cyclohexanones yields predominantly the more stable equatorial alcohols, whereas axial isomers are obtained in the reaction of hindered cyclohexanones.[2] These additions, and particularly hydride reductions, were discussed on the basis of empirical rules[3] named "product development control" and "steric approach control." Explanations of the stereochemistry of these reactions based on pure steric approach considerations[4] or on eclipsing effects[5] were also advanced. Recent kinetic work[6] had shown that hydride reductions yielding the more stable equatorial alcohol predominantly, and previously assumed to be determined by the stability of the products, are in fact kinetically controlled.

Methylenecyclohexanes have a structure similar to that of cyclohexanones. Reduction of the latter compounds with diborane was shown[7] to give a similar distribution of isomeric cyclohexanols to that found in the product of their reaction with metal hydrides. However, the mechanism of this reduction[7] is different from that of hydrogenation,[8] the last reaction being first order in diborane,[8] whereas the reduction is three-halves order in diborane. It was therefore of interest to compare the stereochemistry of the reduction of cyclohexanones with that of the hydroboration of methylenecyclohexanes. The stereochemistry of the hydroboration of the exocyclic olefins 3-methyl- (Ia) and 4-methylmethylenecyclohexanes (IIa) and 3-*t*-butyl- (Ib) and 4-*t*-butylmethylenecyclohexanes (IIb) was studied to this effect.



I II III IV V VI

a, R = CH_3
b, R = $C(CH_3)_3$

These compounds were prepared by the method of Corey[9] from the corresponding cyclohexanones.

The distribution of the isomeric alcohols III–VI, obtained after oxidation of the products of hydroboration, is recorded in Table I.

The products of the reactions were analyzed by glpc and compared with samples of the alcohols IIIa, IIIb, IVa, IVb, Va, Vb, VIa, and VIb that were prepared by reduction of the methyl- or *t*-butylcyclohexanecarboxylic acids.

The less stable product was formed preferentially in the reaction of diborane with the compounds Ia, Ib, IIa, and IIb. The steric course of hydroboration was therefore different from the stereochemistry of the reduction of cyclohexanones,[7] as well as were their kinetics.[7,8] These results showed that the stability of the isomers did not determine the composition of the product of hydroboration and kinetic effect were apparently more important. The approach of diborane to the double bond was easier from the equatorial side, whereas the axial approach is generally preferred during the diborane or metal hydride reduction of unhindered cyclohexanones.

Possible reasons for the difference in approach in hydroboration and reduction, despite the fact that both reactions are kinetically controlled,[7,8] are the difference in the corresponding transition states[10] of the distances of the attacking molecules from the axial hydrogens on the carbons at positions 2 and 6 or 3 and 5, respectively (difference in steric interaction[4]), or from the C–H bonds at the positions 2 and 6 (eclipsing effects[5]). It seems, however, that different torsion effects derived from different points of attack by diborane in the hydroboration and reduction play an important role in the determination of their steric course. During the reductions of cyclohexanones it is the ring carbon that is attacked by diborane and the angle of torsion between the C–O bond and the two equatorial C–H bonds on the neighboring carbons diminishes and is close to zero in the transition state of an equatorial attack[11] (that gives the axial alcohol). This transition state is therefore less favorable than that for axial attack in reduction, where this angle of torsion increases to a more staggered conformation. On the other side, hydroboration proceeds by a four-center transition state in which the boron–carbon link is more developed than the forming carbon–hydrogen bond.[8,12] The boron atom begins to attach itself to the exocyclic carbon in the transition state of the hydroboration of methylenecyclohexanes, and the ring carbon retains its original trigonal geometry without appreciable change in torsion angles. Torsion effects should therefore discriminate very slightly between the two possible

(1) Taken from the M.S. Thesis of D. Lichtenberg, The Hebrw University, 1967.

(2) For a review see A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962).

(3) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

(4) J. C. Richer, *J. Org. Chem.*, **30**, 324 (1965).

(5) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205, (1968).

(6) J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *ibid.*, 6127 (1968).

(7) J. Klein and E. Dunkelblum, *Tetrahedron*, **23**, 205 (1967).

(8) J. Klein, E. Dunkelblum, and M. Wolff, *J. Organometal. Chem.*, **7**, 377 (1967).

(9) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(10) J. A. Marshall and R. D. Caroll, *ibid.*, **30**, 2748 (1965).

(11) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 699, 701 (1967).

(12) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962.

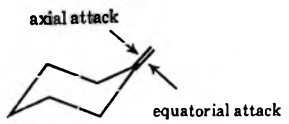
TABLE I

PRODUCTS OF HYDROBORATION[a] OF METHYLENECYCLOHEXANES

Starting material	Hydroboration agent	Yield, %, of alcohols	% *cis* in product	% *trans* in product
Ia	Diborane	76	37 IIIa	63 IVa
IIa	Diborane	82	66 Va	34 VIa
Ib	Diborane	78	33 IIIb	67 IVb
IIb	Diborane	75	68 Vb	32 VIb
Ia	Dicyclohexylborane	58	43[b] IIIa	42[b] IVa
IIa	Dicyclohexylborane	62	42[c] Va	45[c] VIa
Ia	Dichloroborane	68	34 IIIa	66 IVa
IIa	Dichloroborane	66	68 Va	32 VIa

[a] In THF. [b] 15% additional product was formed. [c] 13% additional product was formed.

modes of attack during hydroboration. A similar picture is obtained, when the formation of a complex[8,13] between borane and the olefin is the rate-determining step. However, torsion interactions alone could explain statistical distribution of the two products, but not the predominant formation of the axial isomer during hydroboration and an additional effect is necessarily present to account for this result. It seems to us that the concept of Zimmerman[14] on the favored protonation of exocyclic enols from the equatorial side can be applied in our case, and the protonation is a good model for reactions where torsion effects are small owing to a small degree of bond formation in the transition state and where steric interactions have a predominant influence. Equatorial approach of diborane is from the outside of the fold formed by the exocyclic methylene and the ring VII, whereas the axial attack is from the inside of the fold and is the more hindered of the two. The shift of the attacking reagent from the ring carbon toward the exocyclic carbon increases even more the difference in the energies of the two transition states in favor of the equatorial attack[15] owing to steric interaction of the reagent with the ring hydrogens. This discussion assumes a structure of the methylenecyclohexane part of the transition state of hydroboration that is essentially similar to that of the olefin. This structure is supported by the strong steric interference during hydroboration of cyclohexenes having an axial methyl at the 4 position,[16-19] and even of an axial hydrogen geminal to a *t*-butyl group at this position.[19]



VII

Only chair conformations of methylenecyclohexanes were considered in agreement with the nmr spectrum of the parent compound.[20,21]

A similar analysis of the direction of attack of cyclohexyl radicals in terms of torsion interactions was published recently.[22]

The ratio of the two isomers formed during the studied hydroboration reactions were not identical for all compounds, and the small differences in this ratio can be rationalized in terms of the relative proportions of various chair conformations in which the starting materials exist and the interference of axial substituents in the 3 position to hydrocarbon *cis* to them[16,19]

It is interesting that dichloroborane gave similar ratios of isomers to those formed in the reaction with diborane, but dicyclohexylborane gave almost equal amounts of the two isomeric products. The bulk of the hydroborating agent[23] appears to have an effect in this case, and this effect may be due to the interaction with the substituents on the carbons at positions 2 and 6. However, this evidence is not clear-cut, since the yield in this reaction is lower than in the previous reactions and, in addition, a third compound was formed. Its structure was not established, but it might be an isomer formed by addition, elimination, and a further addition of dicyclohexylborane. Since the elimination reaction could proceed with different rates from the two isomeric boranes formed in the first step, the final composition of the product might not reflect the steric course of the initial reaction.

Experimental Section

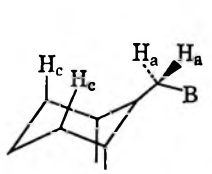
3-Methylcyclohexanone and 4-methylcyclohexanone were commercial products (Fluka). 3-*t*-Butylcyclohexanone[24] and 4-*t*-butylcyclohexanone[25] were prepared by published methods.

3-Methylmethylenecyclohexane (Ia).—NaH, 4.8 g of a 50% suspension in mineral oil, was washed with dry pentane. Dimethyl sulfoxide (DMSO) (50 ml) was then added and the mixture was heated for 1 hr at 70°[9] and then cooled in an ice bath, and a solution of 35.7 g of methyltriphenylphosphonium bromide[26] in 100 ml of DMSO was added dropwise. The red solution so formed was stirred for 15 min at room temperature; then 11 g of 3-methylcyclohexanone was added dropwise over 15 min.

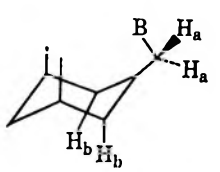
(13) A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).

(14) For a recent discussion see H. E. Zimmerman and P. S. Mariano, *J. Amer. Chem. Soc.*, **90**, 6091 (1968).

(15) A referee suggested a different explanation for the stereochemistry of these hydroborations: "When the reagent approaches the terminal carbon, the hydrogen atoms attached to the carbon are pushed out of the plane while little change occurs in the planar geometry of the inner carbon. Of the two possible approaches shown below, molecular models suggest that I is more favored by 0.2–0.6 kcal/mol because nonbonded hydrogen repulsions between H_a and H_c in I are smaller than those between H_a and H_b in II." We think that this explanation is not correct



I



II

for several reasons. It does not conform to what we know on the transition state of the hydroboration reaction, which has a structure similar to that of the starting olefin as shown by a ρ close to zero (hydroboration of substituted styrenes[8]) and the interference of axial substituents during hydroboration of cyclohexenes.[16] Even assuming the transition states I and II proposed by the referee, the repulsive interaction between H_a and the equatorial hydrogens in positions 2 and 6 in I will be greater than between H_a and H_b or H_c in I and II, respectively. It seems also that these interactions are rather of attractive than of repulsive nature. Our view is that it is the diborane which interferes differently with the ring at its both sides and not the hydrogens of the methylene group.

(16) J. Klein, E. Dunkelblum, and D. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).

(17) M. Nussim, Y. Mazur, and F. Sondheimer, *ibid.*, **29**, 1120 (1964).

(18) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964).

(19) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).

(20) J. T. Gerig, *J. Amer. Chem. Soc.*, **90**, 1065 (1968).

(21) F. R. Jensen and B. H. Beck, *ibid.*, **90**, 1066 (1968).

(22) F. R. Jensen L. H. Gale, and J. E. Rodgers, *ibid.*, **90**, 5793 (1968).

(23) H. C. Brown and G. Zweifel, *ibid.*, **82**, 3222 (1960); **83**, 1241 (1961).

(24) J. Sicher, F. Sipos, and M. Tichy, *Collect. Czech. Chem. Commun.*, **27**, 2907 (1962).

(25) M. Tichy, F. Sipos, and J. Sicher, *ibid.*, **26**, 847 (1961).

(26) A. Maercker, *Org. Reat.*, **14**, 1270 (1965).

The mixture was stirred for an additional hour and the product was distilled directly from this solution at 58° (25 mm). Redistillation gave 8.4 g (77%) of pure Ia: bp 118° ; ir (liquid film) 890 cm^{-1} (C=CH_2).

Anal. Calcd for C_8H_{14}: C, 87.27; H, 12.73. Found: C, 87.55; H, 12.90.

4-Methylmethylenecyclohexane.[27]—Similar treatment of 4-methylcyclohexanone gave IIa: 78% yield; bp 120°; ir (liquid film) 890 cm^{-1} (C=CH_2).

3-*t*-Butylmethylenecyclohexane (Ib) was prepared analogously in 63% yield from 3-*t*-butylcyclohexanone. However, the product was not distilled directly from the reaction mixture, but water (1 l.) and pentane (250 ml) were added, and the mixture was stirred for 15 min and filtered from the precipitate. The layers were separated, the aqueous layer was extracted twice with pentane, and the combined pentane solutions were washed twice with a saturated aqueous solution of NaCl and filtered through a column containing 25 g of alumina. The solvent was removed and the residue was distilled giving Ib: 63% yield; bp 78° (15 mm); ir (liquid film) 886 cm^{-1} (C=CH_2).

Anal. Calcd for $C_{11}H_{20}O$: C, 86.84; H, 13.15. Found: C, 86.71; H, 12.98.

4-*t*-Butylmethylenecyclohexane (IIb).—Similar treatment of 4-*t*-butylcyclohexanone gave IIb: 65% yield; bp 90° (25 mm);[28,29] ir (liquid film) 888 cm^{-1} (C=CH_2).

3-Methylcyclohexanecarboxylic acids were prepared by known procedures.[30] The *cis* acid (mp 28°) was obtained pure, but the *trans* was contaminated with the *cis* product.

***cis*-4-Methylcyclohexanecarboxylic acid** had mp 28° (lit.[31,32] 28–30°). The *trans* isomer was obtained after equilibration of the mixture of isomers[33] and had mp 109° [lit.[31,32] 110°].

***cis*-3-*t*-Butylcyclohexanecarboxylic Acid.**[31]—Dehydration of 3-*t*-butylcyclohexaneonecyanhydrine[34] followed by acid hydrolysis of the nitrite and hydrogenation of the formed unsaturated carboxylic acid gave, after equilibration and two recristalizations from hexane, the pure acid, mp 95° [lit.[31] 95°]. The *trans* isomer was not isolated pure but was contaminated with the *cis* acid.

***cis*-4-*t*-Butylcyclohexanecarboxylic acid**, mp 117°, and its *trans* isomer, mp 175°, were separated by thiourea.[33,35]

***cis*-3-Methylcyclohexylmethanol (IIIa).**—A solution of 1 g of *cis*-3-methylcyclohexanecarboxylic acid in 10 ml of dry ether was added dropwise to 0.5 g of $LiAlH_4$ in 20 ml of dry ether. The reaction mixture was refluxed for 1 hr; the excess hydride was decomposed with water then 4 *N* H_2SO_4, and extracted twice with 10-ml portions of ether. The combined ethereal solutions were washed with water, aqueous KOH, and then again with water. Distillation gave 0.6 g of IIIa, bp 110° (20 mm).

In a similar manner we prepared *trans*-3-methylcyclohexylmethanol (IVa) (contaminated with the *cis* isomer), bp 110° (20 mm); *cis*-4-methylcyclohexylmethanol[32,36] (Va), bp 100° and (15 mm), and its *trans* isomer[32,26] (VIa), bp 108° (20 mm); and *cis*-4-*t*-butylcyclohexylmethanol[32] (Vb), mp 56° (ethanol 80%), and its *trans* isomer[36] (VIb), bp 130° (20 mm).

***cis*-3-*t*-Butylcyclohexylmethanol (IIIb).**—To a stirred solution of 0.2 g of *cis*-3-*t*-butylcyclohexanecarboxylic acid in 5 ml of THF was added dropwise 3 ml of a 2.5 *M* solution of borane in THF. The solution was stirred for 2 hr and 3 ml of water was added; then the solution was stirred for 1 hr, the layers were separated, the aqueous layer was extracted three times with 10-ml portions of ether, and the combined ether layers were washed twice with 10 ml of saturated sodiumbicarbonate solution, dried over magnesium sulfate, and distilled, giving 130 mg of IIIb, bp 130° (20 mm).

Hydroboration Reactions.—A solution of 0.1 mol of the olefin in 100 ml of THF was added dropwise to a cooled solution of 0.25 mol of borane in THF. The reaction mixture was stirred 1 hr at 0°, then 2 hr at room temperature. Excess diborane was decomposed by dropwise addition of water (100 ml). A 3 *N* solution of NaOH (100 ml) was then added, followed by dropwise addition of 30% H_2O_2 (100 ml). The reaction mixture was stirred for 1 hr at room temperature and K_2CO_3 (20 g) was then added. The layers were separated, the aqueous solution was extracted three times with 100 ml of ether, and the combined organic layers were washed with water, dried over magnesium sulfate, then distilled, and analyzed by glpc.

In the dichloroborane reactions, only 0.1 mol of this hydroboration agent was used for each 0.1 mol of olefin. Dichloroborane was prepared by dissolution of 0.1 mol of BCl_3 in 20 ml of THF at 0° followed by addition of 0.05 mol of a solution of borane in THF. This solution was left at 0° for 10 hr before use.

Dicyclohexylborane was prepared by addition of 10 g ($^1/_3$ mol) of cyclohexene to 26 ml of 2.5 *M* solution of borane in THF ($^1/_6$ mol). The solution was left for 16 hr at room temperature before use.

Gas chromatography of the methylenecyclohexanes was carried out on a 3 m × $^1/_8$ in. column of Porapak Q. The products of hydroboration were analyzed on a 3 m × 0.25 in. column of 10% Ucon Polar on Chromosorb P at 140°, or on 4 m × 0.25 in. column of 10% polyneopentyl glycol succinate or Chromosorb P at 170°. The ketones I and II were used as internal standards in the reaction mixture for quantitative determination of yields. The yields of the reactions were also determined directly by distillation of the products. The analyses of the obtained mixtures of isomers were in agreement with their formulas.

Registry No.—Ia, 3101-50-6; Ib, 24452-96-8; IIa, 2808-80-2; IIb, 13294-73-0; IIIa, 24453-33-6; IIIb, 24453-34-7.

(27) J. F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Amer. Chem. Soc.*, **82**, 6090 (1960).

(28) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).

(29) B. Cross and G. H. Whitham., *J. Chem. Soc.*, 3892 (1960).

(30) L. H. Darling, A. K. Macbeth, and J. A. Mills, *ibid.*, 1364 (1953).

(31) M. Tichy, J. Jonas, and J. Sicher, *Collect. Czech. Chem. Commun.*, **24**, 3434 (1959).

(32) H. Van Bekkum, A. A. B. Kleis, A. A. Massier, D. Medema, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **80**, 595 (1961).

(33) H. H. Lau and H. Hart, *J. Amer. Chem. Soc.*, **81**, 4897 (1959).

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(35) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Proc. Kon. Ned. Akad. Wetensch. Ser. B62*, No. 3, 147 (1959); *B64*, 161 (1961).

(36) N. Mori, *Bull. Chem. Soc. Jap.*, **34**, 1299 (1961).

The Acid-Promoted Opening of the Three-Membered Ring in *endo*-6-Methylbicyclo[3.1.0]hexane[1]

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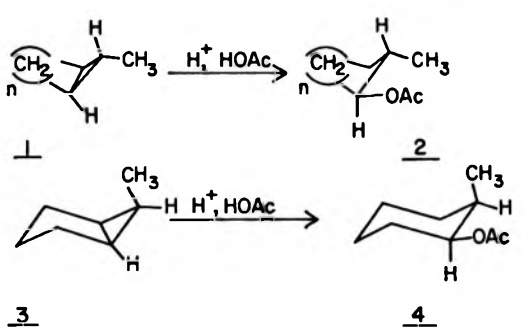
Addition of acetic acid to *endo*-6-methylbicyclo[3.1.0]hexane gives nearly equal amounts of methylcyclopentyl acetate and *cis*-2-methylcyclohexyl acetate. Addition of acetic acid-O-*d* gave methylcyclopentyl acetate containing 1% d_2 labeled species as determined by mass spectral analysis. The d_2 content of the *cis*-2-methylcyclohexyl acetate produced in the same reaction was assumed to be the same. The stereoselectivity of acetate formation in the cleavage of the bond common to both rings is reflected in the 47:2 ratio of *cis*-/*trans*-2-methylcyclohexyl acetate. These results are compared with earlier studies of the acid-promoted opening of *exo*-6-methylbicyclo[3.1.0]hexane. The mechanistic rationale for these results is discussed in terms of bond-protonated or carbon-bridged intermediates.

Stereoselectivity in the acid-promoted addition of acetic acid across the internal strained bond of bicyclo[*n*.1.0] alkanes has been observed for *exo*-7-methylbicyclo[4.1.0]heptane (**1**, $n = 4$) and *exo*-6-methylbicyclo[3.1.0]hexane (**1**, $n = 3$).[2] Respectively, *trans*-2-methylcycloheptyl (**2**, $n = 4$) and *trans*-2-methylcyclohexyl (**2**, $n = 3$) acetates were by far the predominant acetates produced in the internal mode of cleavage.



In order to learn whether internal cleavage is truly stereoselective or not, the acid-promoted addition of acetic acid to *endo*-6-methylbicyclo[3.1.0]hexane (**3**), has been studied. Should cleavage of the internal bond of **3** and resulting acetate formation again occur with inversion, *cis*-2-methylcyclohexyl acetate (**4**) would be expected.

Results

The treatment of *endo*-6-methylbicyclo[3.1.0]hexane with 0.09 *N* sulfuric acid in glacial acetic acid at 47° for 26 hr gave a product mixture containing 11% olefins and 89% acetates as determined by gas–liquid partition chromatography (glpc). Further glpc analysis of the olefin mixture demonstrated the presence of 1-methylcyclohexene, 1-ethylcyclopentene, and 3-methylcyclohexene in the relative percentages given in Table I. These olefins were identified by gas chromatographic retention times using two different columns. In addition 1-methylcyclohexene, the predominant olefin, was isolated by preparative glpc and identified by comparative infrared (ir) and nuclear magnetic resonance (nmr) spectra. No detectable peaks corresponding to the retention times of ethylidenecyclopentane, 3-ethylcyclopentene, vinylcyclopentane, or unconverted 6-*endo*-methylbicyclo[3.1.0]hexane could be found in the chromatograms.

The mixture of acetates was not analyzed directly but was converted, by lithium aluminum hydride hydrogenolysis, to a mixture of alcohols which was more readily separated by glpc than the mixture of acetates. The alcohol mixture consisted of methylcyclopentylcarbinol, *cis*-2-methylcyclohexanol, *trans*-2-methylcyclohexanol, *cis*-2-ethylcyclopentanol, and *trans*-2-ethylcyclopentanol in the relative percentages given in Table I. Methylcyclopentylcarbinol and *cis*-2-methylcyclohexanol, the two major alcohols, were separated by preparative glpc and identified by comparative ir.

The ring-opening solvolysis of *endo*-6-methylbicyclo[3.1.0]hexane was repeated using 0.09 *N* deuteriosulfuric acid in acetic acid-O-*d* solution. The deuterated acids were used primarily to ascertain the degree of reversible protonation prior to cyclopropyl bond cleavage and the extent of olefin to acetate conversion. Glpc analyses showed the distribution of acetates (alcohols) and olefins as given in the second row of Table I. The mixture of alcohols was oxidized to a mixture of ketones which consisted of two major components as revealed by glpc. These were separated and identified as methylcyclopentyl ketone and 2-methylcyclohexanone by comparative glpc and mass spectra. 1-Methylcyclohexanol, clearly distinguishable from the ketones by gas chromatography, could not be detected in the chromatogram of the mixture of ketones.

The isotopic distribution of the labeled methycyclopentylcarbinol was 17% d_0, 82% d_1, and 1% d_2 and was assumed to be the same for labeled *cis*-2-methycyclohexanol. The latter was not isolated for mass spectral isotopic analysis because of anticipated difficulty in obtaining a meaningful isotopic analysis when $M^+ - 1$ becomes significantly large relative to a low intensity M^+ peak, as is frequently the case for cyclohexanols. The isotopic distribution of methylcyclopentyl ketone was 16% d_0, 83% d_1, and 1% d_2 before, and 17% d_0, 83% d_1, and 0% d_2 after sodium methoxide–methanol exchange. For 2-methylcyclohexanone, the distribution was 19% d_0, 80% d_1, and 1% d_2 before, and 20% d_0, 80% d_1, and 0% d_2 after exchange.

A further test of the kinetic control of acetate formation was the observation that neither methylcyclo-

(1) (a) Paper VIII in a series dealing with carbon–carbon bond fission in cyclopropanes. (b) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this work. Acknowledgment is also made to the National Science Foundation for assistance in the purchase of the mass spectrometer used in this study.

(2) R. T. LaLonde and M. A. Tobias, *J. Amer. Chem. Soc.*, **86**, 4068 (1964).

Table I

Product Distribution from *endo*- and *exo*-6-Methylbicyclo[3.1.0]hexane on Acid-Promoted Acetolysis[a]

	Acetates (alcohols), 100%							Olefins, 100%			
Reactant	Acetate, %	AcO	OAc *cis*	OAc *trans*	OAc *cis*	OAc *trans*	Olefin, %				
3[b]	89	48	2	1	47	2	11	0	14	80	7
3[c]	86	49	2	1	46	2	14	0	17	77	7
1 (n = 3)[d]	80	52	2	7	2	37	20	1	27	55	18

[a] The accuracy of the distributions is qualified by the lack of control experiments to determine the degree of fractionation of olefins and acetates occurring in work-up. [b] Glacial acetic acid, 0.09 N sulfuric acid, 47°, 26 hr. [c] Acetic acid-O-d, 0.09 N deuteriosulfuric acid, 47°, 26 hr. [d] Reference 2.

pentylcarbinyl acetate nor *cis*-2-methylcyclohexyl acetate is isomerized on treatment with 0.09 N sulfuric acid in glacial acetic acid at 47°.

The reactivities of two of the olefins produced from **3** were assessed. Treatment of 1-methylcyclohexene with 0.09 N sulfuric acid in acetic acid at 47° for 26 hr resulted in a 6% conversion to 1-methylcyclohexyl acetate. Similar treatment of 3-methylcyclohexene for 52 hr resulted in less than 5% conversion to acetates which consisted of 1% methylcyclopentylcarbinyl acetate, 17% 2-methylcyclohexyl acetate, and 82% 3-methylcyclohexyl acetate. The relative amounts of these acetates and their identities is based on mass spectral analysis of the mixture of alcohols, obtained on lithium aluminum hydride hydrogenolysis of the acetates, and mass and infrared spectral and gas chromatographic analysis of the corresponding mixture of ketones.

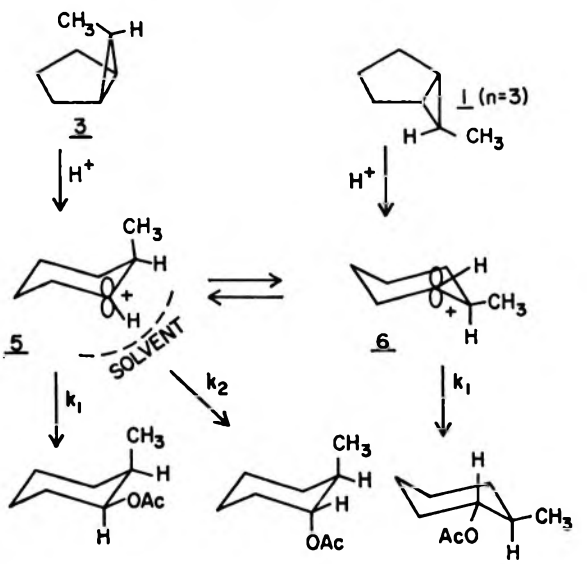
Discussion

The product analyses as summarized in Table I reveal that internal bond rupture in **3** gives *cis*- and *trans*-2-methylcyclohexyl acetate in a ratio of 47:2. The results of earlier work with the isomeric 6-*exo*-methylbicyclo[3.1.0]hexane (**1**, n = 3) are also summarized in Table I and show a somewhat lower degree of stereospecificity, the ratio of *trans* to *cis* acetate being 37:2.

The results of the ancillary experiments indicate that acetates are formed directly by addition of acetic acid across the internal bond of **3**. Thus the absence of 1-methylcyclohexyl acetate formation as well as multiple deuterium labeling show that acetates are not formed competitively by addition to the olefins produced. The low level of olefin reactivity, relative to the bicycloalkane **3**, is also demonstrated. Less than 10% of 1- and 3-methylcyclohexene are converted to acetates under conditions which completely transform **3** to acetate. Finally, the demonstrated stability of the two major acetates, *cis*-2-methylcyclohexyl acetate and methylcyclopentylcarbinyl acetate, shows that the acetate distribution represents largely the products generated directly in the ring cleavage step. Relevant confirmatory evidence comes from an earlier observation. When ring cleavage of bicyclo[3.1.0]hexane was carried out in 0.07 N sulfuric acid at 47°, the distribution of acetates remained constant for reaction periods of 0.5, 1.0, 41, and 61 hr.[3] When cleavage of bicyclo[4.1.0]heptane was carried out under the same conditions, the acetate distribution remained constant for reaction periods of 0.5, 1.0, 24 and 86 hr.[3]

The observed stereospecificity of acetate formation in internal bond cleavage clearly is inconsistent with a mechanism involving equilibrating 2-methylcyclohexyl carbonium ions (Scheme I). If equilibrating 2-methylcyclohexyl carbonium ions, **5** and **6** had been involved, both 6-methylbicycloalkanes would have furnished the same mixture of acetates.

Scheme I



Other variations of a secondary carbonium ion rationale would also be inconsistent with results. An unsymmetrically solvated carbonium ion (**5**), one in which the solvent is associated with the side of the ring opposite the methyl group, could possibly account for stereoselectivity, but such a carbonium ion would lead on collapse (k_2) to the *trans*, not the *cis* isomer. Assuming symmetrical solvation of the carbonium ion **5**, a slight predominance of the *cis* acetate could be expected on the basis of the nearly fourfold preference[4,5] for equatorial (k_1) over axial (k_2) attack of a chair cyclohexyl carbonium ion. Reasonably, the estimated preference for equatorial solvolysis would be even less than fourfold in the case of **5** because of the obstruction to equatorial attack by the adjacent axial methyl group. The observed preference for *cis* over *trans* acetate formation from **3** is 47:2, a ratio much in excess of what could be expected from equatorial solvent attack of **5**. Moreover should the principal pathway to 2-methylcyclohexyl acetates involve a carbonium ion

(3) R. T. LaLonde and L. S. Forney, *J. Amer. Chem. Soc.*, **85**, 3767 (1963).

(4) J. A. Berson and P. Reynolds-Warnhoff, *ibid.*, **86**, 595 (1964).

(5) A. Streitweiser and C. E. Coverdale, *ibid.*, **81**, 4275 (1959).

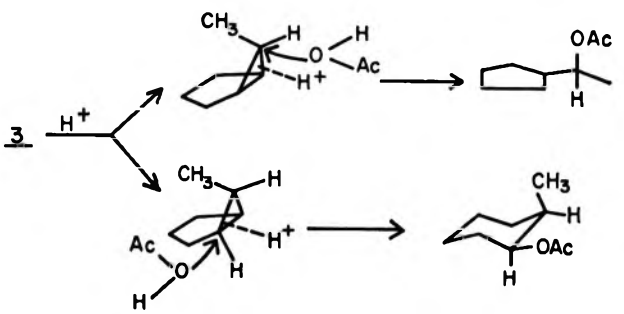
intermediate, then solvolysis of **1** (n = 3) occurring with preferential equatorial attack of carbonium ion **6** would be expected to give a *trans* to *cis* ratio of nearly four, but the observed ratio is 37:2. Nevertheless, while a carbonium ion pathway does not appear to be the major one, it cannot be dismissed altogether. The formation of some *trans*-2-methylcyclohexyl acetate from **3** and *cis*-2-methylcyclohexyl acetate from **1** (n = 3) suggests the involvement of a carbonium ion process competing to a minor degree with a more stereospecific one.

Besides stereospecificity, there are two other features of the ring opening of **3** which should be considered in attempting to formulate a mechanistic rationale. One of these is the distribution of acetates resulting from internal and external modes of bond rupture. In the case of **3**, 50% of the acetates arise from external bond cleavage and 50% arise from internal cleavage. By comparison, the *exo*-methyl isomer **1** (n = 3) produces 39% of the acetates by internal bond rupture and 61% by external rupture.

The other feature of the acetate distribution to be considered is the disparity of acetates arising from two possible modes of external cleavage. As the data in Table I illustrates, methylcyclopentylcarbinyl acetate formation far exceeds the formation of 2-ethylcyclopentyl acetate. Possibly the predominance of methylcyclopentylcarbinyl acetate formation might be attributed to a relatively larger number of low energy pathways leading to this type of product. Conceivably one such additional pathway could involve a carbonium ion–ring contraction route. However, this route to cyclopentylcarbinyl acetate does not seem likely on the basis of known structural requirements for ring contraction. Goering[6] has pointed out that ring contraction is involved in the dehydration of equatorial cyclohexanols if C_2 is substituted with (1) two alkyl groups, (2) an alkyl group and a hydroxyl group, (3) a hydroxyl group, or (4) a phenyl group. Evidently a single alkyl substituent is insufficient for contraction. There are numerous other examples which illustrate that the potential leaving group must be *trans* coplanar to the migrating carbon atom. Acetolysis of *trans*-2-phenylcyclohexyl tosylate produces 40% ring-contracted product but less than 2% of this type of product results from the acetolysis of *cis*-2-phenylcyclohexyl acetate.[7] No ring contractions have been observed in the acetolysis of either *cis*- or *trans*-2-alkylcyclohexyl tosylates,[8,9] although deamination of *trans*-2-methylcyclohexyl amine in aqueous acetic acid gives about 7% ring-contracted olefin[10] and 10% ring-contracted alcohol. The bicyclo[n.1.0]alkanes possess neither the substituent nor stereochemical requirement for contraction,[11] and therefore the ring contraction route to methylcyclopentylcarbinyl acetate seems remote. In connection with the consideration of rearrangement routes to products, it should be mentioned that the stereospecificity in 2-methylcyclohexyl acetate formation could not be accounted for by the reverse rearrangement, *i.e.*, a ring expansion–carbonium ion route.

The three features of the acetate distribution which must be accounted for are stereospecificity, the disproportionately large extent of internal bond rupture, and the preference for the formation of methylcyclopentylcarbinyl acetate resulting from the external mode of rupture. Possibly one way to account for these reactivity characteristics is by nucleophilic solvent attack of bond-protonated intermediates as postulated earlier[2,3,12,13] and depicted in Scheme II. According to this interpretation, the ratio of the two predominating

Scheme II



acetates would, for the most part, reflect the populations of externally and internally protonated intermediates. In terms of the bond-protonated species, the greater degree of internal rupture in **3** can be attributed to the greater strain of the internal bond in **3**, relative to that of **1** (n = 3), which results from the crowding of methyl and trimethylene ring hydrogens. The direct relationship between the extent of internal cleavage and strain has already been noted in connection with earlier work.[14] For example, bicyclo[2.1.0]pentane, which possesses a severely strained internal bond,[15] undergoes only internal bond cleavage.[3] In contrast the ratio of total acetates produced by internal and external bond rupture in *exo*-methylbicyclo[4.1.0]heptane, **1** (n = 4), is 32:68,[2] a value close to the statistical ratio of 33:67.

An explanation to account for the preference for methylcyclopentylcarbinyl acetate formation in the external mode of cleavage may lie in the greater accessibility of C_6 than C_1 to an approaching nucleophile. An examination of a model of **3** and **1** (n = 3) shows that hydrogens lying beneath the trimethylene ring (C_2, C_3, and C_4) make backside approach at the bridgehead positions more difficult than the same mode of approach to C_6.

Alternatively, carbon-bridged intermediates, as depicted in Scheme III, possibly might be used to explain the formation of methylcyclopentylcarbinyl and *cis*-2-methylcyclohexyl acetates, although the role of such intermediates has been discounted in the deamination of propyl amines and in the addition of sulfuric acid to cyclopropane.[16] To the extent that such intermediates are generated from **1** (n = 3) and **3** (Scheme III) in the

(6) H. L. Goering, R. L. Reeves, and H. H. Espy, *J. Amer. Chem. Soc.*, **78**, 4926 (1956).

(7) S. A. Roman and W. D. Closson, *ibid.*, **91**, 1701 (1968).

(8) H. L. Goering and R. L. Reeves, *ibid.*, **78**, 4831 (1956).

(9) W. Hückel and C. M. Jennewien, *Justus Liebigs Ann. Chem.*, **683**, 100 (1965).

(10) W. Hückel and M. Hanack, *Angew. Chem., Int. Ed. Engl.*, **6**, 534 (1967).

(11) In the bicyclo[n.1.0]alkanes, the potential leaving group, a strained carbon–carbon bond, is *cis* to the migrating carbon atom.

(12) R. T. LaLonde and M. A. Tobias, *J. Amer. Chem. Soc.*, **85**, 3771 (1963).

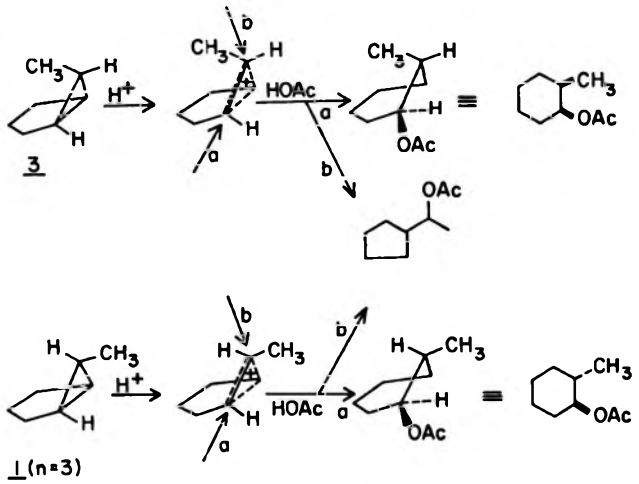
(13) For other references, see C. J. Collins, *Chem. Rev.*, **69**, 541 (1969).

(14) R. T. LaLonde and L. S. Forney, *J. Org. Chem.*, **29**, 2911 (1964).

(15) R. B. Turner, P. Goebel, B. J. Mallon, W. von E. Doering, J. F. Coburn, Jr., and M. Pomerantz, *J. Amer. Chem. Soc.*, **90**, 4315 (1968).

(16) For a review see the source given in ref 13.

Scheme III



slow step of a two-step sequence, equal amounts of methylcyclopentylcarbinyl and 2-methylcyclohexyl acetates should be formed, but actual amounts of the two acetate types produced from **1** (n = 3) and **3** could also reflect the factors of relative strain relief and selective obstruction to nucleophilic solvent attack, even though the second step be the faster of the two. Since the importance of the relief of strain and the selective obstruction to nucleophilic attack cannot be assessed, the influence of these two factors in altering the product distribution from carbon-bridged ions cannot be known. Consequently, a distinction between carbon-bridged and bond-protonated mechanisms cannot be made on the basis of the product analysis reported here.

Experimental Section

Spectra were obtained as follows: nmr, in CCl_4, 2% TMS (τ 10) using a Varian A-60A spectrometer; ir, in CCl_4 using a Perkin-Elmer 137 spectrometer; mass using a Hitachi Perkin-Elmer RMU6 spectrometer with all glass heated inlet, chamber temperature 165°, 70eV.

Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected and were determined on a Mel-Temp apparatus. Glpc analyses were obtained on a Varian Aerograph Model 200 using helium as the carrier gas and the columns indicated.

Materials.—Acetic acid-*O*-*d* was prepared from acetic anhydride and D_2O. The D_2SO_4 was purchased from Merck and Co. Ltd. 1-Methylcyclohexene, methylcyclopentylcarbinol, 2-methylcyclohexanone, and methylcyclopentyl ketone were purchased from the Aldrich Chemical Company and purified. *cis*- and *trans*-2-methylcyclohexanol were prepared by the method of Eliel and Lukach.[17] All other olefins and cycloalkanols used as authentic comparison samples were prepared earlier[18] by well-known procedures.

***endo*-6-Methylbicyclo[3.1.0]hexane (3). A. From Bicyclo[3.1.0]hexane-*endo*-6-carboxylic Acid.**—The title acid was prepared by the method of Meinwald, Labana, and Chadha,[19] mp 83–84°. A 15.5-g sample of the acid (0.12 mol) in 100 ml of anhydrous ether was added dropwise to 5.6 g (0.15 mol) of $LiAlH_4$ in 250 ml of ether. After heating to reflux for 5 hr, the mixture was cooled, water was added cautiously, and 100 ml of 4 N H_2SO_4 was added to dissolve the salts. The aqueous layer was extracted with ether. The combined extracts were washed successively with water, 5% aqueous $NaHCO_3$, and saturated brine, and then dried ($MgSO_4$). The ethereal extract was concentrated and distilled giving 12.5 g (83.5%) of *endo*-6-hydroxymethylbicyclo[3.1.0]hexane: mp 86–87° (12 mm), reported[20] 79–85° (9 mm); ir 3300 (OH), 2950 (CH), 1025 cm^{-1} (CO); nmr 6.41 (s, 1, D_2O exchangeable and concentration dependent, OH), 6.55 (d, 2, J = 1.8 Hz, CH_2OH), 7.8–9.3 (m, 9 H); 3,5-dinitrobenzoate mp 103–104° (from EtOH), reported[20] 102.5–103.8°.

endo-6-Hydroxymethylbicyclo[3.1.0]hexane, 11 g (0.10 mol), was added to 7 g (0.085 mol) of aluminum isopropoxide. The stirred mixture was heated at 95° until all the isopropyl alcohol had distilled. Twenty grams of freshly distilled anisaldehyde was added and the mixture was maintained at 120° and 10 mm for 1 hr in a distillation apparatus. The 7 g of colorless liquid which distilled was then redistilled giving 5 g (47%) of bicyclo[3.1.0]hexane-6-carboxaldehyde: bp 63–65° (10 mm); ir 3130, 3090, 2990 (CH), 1700 (CH=O), 1210, 1100, 935 cm^{-1}; nmr τ 0.55 (d, 1, J = 5.2 Hz, CH=O), 7.7–8.7 (m, 9 H). The aldehyde was stored at Dry Ice temperature since it was unstable at room temperature.

Bicyclo[3.1.0]hexane-6-carboxaldehyde, 5.5 g (0.05 mol), 6.5 g of 85% hydrazine hydrate, and 0.2 ml of glacial acetic acid were heated at 120° in a distillation apparatus until water no longer distilled. To the distillation residue was added 0.5 g of powdered sodium hydroxide in 2 ml of triethylene glycol. The resulting mixture was maintained at 160° for 1 hr. During this time 3.5 ml of hydrocarbon distilled. Glpc (8 ft × 0.25 in., 4% squalane on Celite, 80°) showed *exo*- and *endo*-6-methylbicyclo[3.1.0]hexane present in the ratio of 1:7. Preparative-scale glpc gave *exo*-6-methylbicyclo[3.1.0]hexane (**1**, n = 3)[2] and *endo*-6-methylbicyclo[3.1.0]hexane (**3**): ir 3000, 2930, 2860, 1450, 1390, 1330 cm^{-1}; nmr τ 7.9–8.9 (m, 8 H), 9.0–9.2 (m, 4 H).

Anal. Calcd for C_7H_{12}: C, 87.42; H, 12.58. Found: C, 87.65; H, 12.70.

B. From Cyclopentene, Ethylidene Iodide, and Diethylzinc.—According to the procedure of Nishimura, Kawabate, and Furukawa,[21] 9.4 ml of ethylidene iodide (0.1 mol) was added dropwise over a period of 1 hr to a mixture of 3.4 g (0.05 mol) of cyclopentene, 6.0 ml (0.006 mol) of diethylzinc, and 25 ml of hexane under nitrogen. The resulting mixture was heated to reflux for 2 hr, cooled, and poured cautiously into a stirred mixture of 25 ml of 1% aqueous HCl and 20 ml of ether. The aqueous layer was extracted several times with ether. The combined extracts were washed successively with water, 5% aqueous $NaHCO_3$, and saturated brine, and dried ($MgSO_4$). The ethereal extract was concentrated and then distilled giving 1.6 g of hydrocarbon, bp 120–132° (1 atm). Glpc analysis (5 ft × 0.25 in., 20% Se-30, 75°) showed the presence of two components in the ratio of 2:3. The two hydrocarbons were separated by preparative scale gas chromatography. The minor component was identified by comparative ir as the *exo*-6-methyl isomer; the major component displayed the same ir and nmr characteristics as the sample of the *endo*-6-methyl isomer described in part A.

Opening of *endo*-6-Methylbicyclo[3.1.0]hexane. A. With H_2SO_4 and Acetic Acid.—A sealed glass tube containing 0.80 g (8.3 mmol) of *endo*-6-methylbicyclo[3.1.0]hexane, 50 mg of 96% H_2SO_4, and 11.0 ml of glacial acetic acid was maintained at 47° for 26 hr. The reaction mixture was processed as described earlier.[3] In this manner was obtained 1.54 g of yellow oil: ir 1710, 1370, 1240, and 1130 cm^{-1}. This oil contained 11% hydrocarbon, 89% acetate, and some residual ether as determined by glpc (8 ft × 0.25 in., 20% Se-30, 75°).

A 1.50-g sample of the above-described product mixture in 20 ml of anhydrous ether was added to 0.5 g of $LiAlH_4$ in 20 ml of ether, and the resulting mixture was heated to reflux for 2 hr and cooled. Cold water and then 25 ml of 5 N H_2SO_4 were added and the aqueous layer was immediately extracted with ether. The combined ether solutions were washed successively with H_2O, 5% aqueous $NaHCO_3$, and saturated brine, and dried ($MgSO_4$). The bulk of the ether was removed by careful distillation through a 12-in. Vigreux column to give 1.35 g of yellow oil which was added to a column containing 20 g of alumina. Elution of the column with pentane and subsequent careful removal of the solvent by distillation left 150 mg of a colorless mixture of olefins. Continued elution with ether and then methanol and removal of the solvent gave 1.1 g of a colorless mixture of alcohols.

The first glpc analysis of olefins (10 ft × 0.25 in., 30% silver

(17) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).

(18) M. Tobias, Ph.D. Thesis, State University College of Forestry, Syracuse, N. Y., 1965.

(19) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Amer. Chem. Soc.*, **85**, 583 (1963).

(20) K. B. Wiberg and A. J. Ashe, III, *ibid.*, **90**, 63 (1968).

(21) J. Nishimura, N. Kawabata, and J. Furukawa, *Tetrahedron*, **25**, 2647 (1969).

nitrate–triethylene glycol on firebrick, 45°) showed the presence of peaks at 6.9 (80%), 7.6 (7%), and 10.8 min (14%). The retention time of these three peaks in the order given corresponded to 1-methylcyclohexene, 1-ethylcyclopentene, and 3-methylcyclopentene. There was no detectable amounts of ethylidenecyclopentane (7.3 min), 3-ethylcyclopentene (13.4 min), and vinylcyclopentane (14.2 min). The second glpc analysis (10 ft × 0.25 in., 4% squalane on Celite, 65°) showed peaks which corresponded to 3-methylcyclohexene (7.1 min), 1-ethylcyclopentene (8.1 min), and 1-methylcyclohexene (9.6 min). The major peak (80%) at 9.6 min was separated by preparative glpc (10 ft × 0.25 in., 4% squalane on Celite), and its ir and nmr spectra were identical with those of a purified sample of 1-methylcyclohexene. There was no detectable *endo*-6-methylbicyclo[3.1.0]hexane (11 min).

Glpc (11 ft × 0.25 in., 17% triethylene glycol on Celite, 75°) analysis of the mixture of alcohols obtained from the $LiAlH_4$ reduction showed the presence of at least five components: 17.9 (2%), 25.4 (47%), 28.3 (48%), 30.0 (2%), and 31.6 min (1%). These retention times in the order listed correspond to *cis*-2-ethylcyclopentanol, *cis*-2-methylcyclohexanol, methylcyclopentylcarbinol, *trans*-2-methylcyclohexanol, and *trans*-2-ethylcyclopentanol. The two major components were separated by preparative glpc. The ir of the material whose retention time was 25.4 min (47%) was identical with the ir of *cis*-2-methylcyclohexanol. The ir of the material with the retention time of 28.3 min (48%) was identical with an ir of cyclopentylmethylcarbinol.

B. With D_2SO_4 and Deuterioacetic Acid.—A sealed glass tube containing 0.41 g (4.2 mmol) of *endo*-6-methylbicyclo[3.1.0]-hexane, 25 mg of concentrated D_2SO_4, and 6.5 ml of acetic acid-*d* was kept at 47° for 26 hr and then processed as described earlier.[3] Glpc analysis (8 ft × 0.25 in., Se-30, 75°) showed 86% acetate and 14% hydrocarbons.

The mixture of acetate and olefins in ether was converted by $LiAlH_4$ in the manner described in part A to a mixture of alcohols and olefins (0.68 g) containing some ether. Glpc analysis of the olefins (10 ft × 0.25 in., 4% squalane on Celite, 45°) showed three peaks: 9.0 (77%), 7.7 (17%), and 7.0 min (7%). These peaks in the order listed correspond to 1-methylcyclohexene, 1-ethylcyclopentene, and 3-methylcyclohexene.

The glpc analysis of alcohols showed the presence of five components: 17.5 (2%), 24.8 (46%), 28.1 (49%), 29.8 (2%), and 31.3 min (71%). The retention times in the order given correspond to *cis*-2-ethylcyclopentanol, *cis*-2-methylcyclohexanol, methylcyclopentylcarbinol, *trans*-2-methylcyclohexanol, and *trans*-2-ethylcyclopentanol. Methyl cyclopentylcarbinol was separated by glpc: mass spectrum *m/e* 115 (17% d_0, 82% d_1, and 1% d_2).[22]

A cooled solution containing 420 mg of chromic anhydride 620 mg of 96% sulfuric acid in 5 ml of water was added dropwise to 0.65 g of the mixture of alcohols in acetone. The mixture was stirred 30 min and immediately thereafter mixed with 25 ml of ice water and 25 ml of ether. The aqueous layer was extracted with ether. The combined ethereal extract was washed with H_2O, 5% $NaHCO_3$, and saturated brine, and dried ($MgSO_4$). Concentration of the extract gave 0.52 g of yellow liquid which consisted of equal amounts of methylcyclopentyl ketone (4.3 min) and 2-methylcyclohexanone (5.5 min) as determined by glpc (10 ft × 0.25 in., triethylene glycol, 125°). Peaks could not be found at 6.1 and 9.8 min, the retention times of 3-methylcyclohexanone and 1-methylcyclohexanol, respectively. Separation of a small quantity of the ketone mixture by preparative glpc gave methylcyclopentyl ketone, mass spectrum *m/e* 113 (16% d_0, 83% d_1, and 1% d_2), and 2-methylcyclohexanone, mass spectrum *m/e* 113 (19% d_0, 80% d_1, and 1% d_2).

The remaining mixture of ketones, 0.41 g, 2 ml of MeOH, and 0.35 g of NaOMe in a sealed glass tube was kept at 25° for 8 days. Under these conditions 80–90% of any α-deuterium would have been exchanged.[23] The contents of the tube were poured into 25 ml of ice water and 25 ml of ether. The aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, 5% aqueous $NaHCO_3$, and saturated brine, and dried ($MgSO_4$). Concentration of the extract gave 0.33 g of yellow liquid which consisted of only the original two ketones as determined by glpc. Separation of the mixture by glpc (conditions as above) gave methylcyclopentyl ketone [mass spectrum *m/e* (% relative intensity) 113 (67) (17% d_0, 83% d_1, and 0% d_2), 98 (20), 72 (48), 71 (71), 70 (100), 43 (80)] and 2-methylcyclohexanone [mass spectrum *m/e* 113 (83) (20% d_0, 80% d_1, and 0% d_2), 98 (15), 85 (38), 70 (72), 69 (97), 68 (100), 57 (43), 56 (46), 55 (46), 44 (30), 43 (32)].

Treatment of Methylcyclopentylcarbinyl and *cis*-2-Methylcyclohexyl Acetate with Acetic Acid and H_2SO_4.—Methylcyclopentylcarbinyl acetate, 428 mg, 66 mg of concentrated H_2SO_4, and 12 ml of glacial acetic acid were heated at 46° in a sealed glass tube for 26 hr. Thereafter the mixture was processed in the same manner as described for the acetolysis of **3** above. Analysis of the crude acetate by glpc (8 ft × 0.25 in., 20% Se-30, 80°) showed the presence of a trace (<1%) of olefin in addition to acetate. Separation of the ester fraction by glpc gave material whose ir was the same as methylcyclopentylcarbinyl acetate and showed no bands in the regions 10.0–10.3 or 11.0 μ as shown by *cis*- and *trans*-2-methylcyclohexyl acetates. The nmr was identical with that of starting acetate.

cis-2-Methylcyclohexyl acetate, 400 mg, 25 mg of H_2SO_4, and 5.5 ml of glacial acetic acid were kept in a sealed glass tube at 47° for 26 hr. The reaction mixture was processed in the customary manner[3] to give 620 mg of clear liquid containing some ether. This liquid was treated with $LiAlH_4$ in the customary manner to give 580 mg of alcohol showing only one peak on glpc analysis (triethylene glycol) and whose ir was identical with that of *cis*-2-methylcyclohexanol.

Treatment of 1- and 3-Methylcyclohexene with H_2SO_4–Acetic Acid.—1-Methylcyclohexene, 420 mg, 25 mg of concentrated H_2SO_4, and 5.5 ml of glacial acetic acid were heated at 47° in a sealed glass tube for 26 hr. Processing the reaction mixture in the customary manner[3] gave 550 mg of a light yellow liquid which consisted of 94% olefin and 6% acetate as determined by glpc (Se-30). Olefin and acetate (ir, 5.74 μ) components were separated by preparative glpc. The nmr and ir of the olefin and the ir of the alcohol were identical with the corresponding spectra of starting 1-methylcyclohexene and 1-methylcyclohexyl acetate, respectively.

3-Methylcyclohexene, 1 g, 50 mg of concentrated H_2SO_4, and 11 ml of acetic acid were heated at 48° for 52 hr in a sealed glass tube. The reaction mixture was processed in the customary manner[3] to give 1.5 g of a mixture containing 5% acetate, 95% olefin, and some residual ether. This mixture was treated with $LiAlH_4$ in ether in the customary manner to afford, after glpc separation (5 ft × 0.25 in., 15% Carbowax 20M, 130°), 25.2 mg of a mixture of alcohols: mass spectrum *m/e* (% relative intensity) 114 (4), 96 (65), 81 (60), 71 (100), 68 (28), 57 (50), 55 (38), 45 (20). To a cooled solution of 24.2 mg of the mixture of alcohols in 2.5 ml of acetone was added dropwise a solution of 15.4 mg of chromic anhydride and 30.2 mg of concentrated H_2SO_4 in four micro drops of water. The reaction mixture was stirred for 20 min, concentrated at the rotary evaporator, and mixed with 5 ml of ether and 25 ml of water. The aqueous layer was extracted with ether, the combined ether extract was washed with water, 5% aqueous $NaHCO_3$, dried, and concentrated giving 19.6 mg of a mixture of 1% methylcyclopentyl ketone, 17% 2-methylcyclohexanone, and 82% 3-methylcyclohexanone as determined by glpc (5 ft × 0.25 in., 15% Carbowax 20M, 103°): ir 5.84 μ; mass spectrum *m/e* (% relative intensity) 112 (31), 97 (12), 94 (7), 84 (8), 71 (11), 69 (100), 68 (19), 56 (50), 55 (35), 43 (14). Mass spectrum of individual components [*m/e* (relative intensity)]: 3-methylcyclohexanone 112 (28), 97 (12), 94 (7), 84 (5), 69 (100), 58 (10), 56 (48), 55 (29), 43 (8); 2-methylcyclohexanone 112 (44), 97 (29), 84 (29), 69 (48), 68 (100), 56 (58), 55 (49), 43 (13); methylcyclopentyl ketone 112 (25), 97 (10), 84 (3), 71 (54), 69 (78), 56 (1), 55 (5), 43 (100).

Registry No.—**3**, 24903-99-9.

(22) Isotopic distributions were calculated by the method of K. Biemann: "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, pp 224–225.

(23) Unpublished results, J-y Ding.

1,3-Bridged Aromatic Systems. VI.[1,2] 12,13-Benzo-16-bromo[10]metacyclophane

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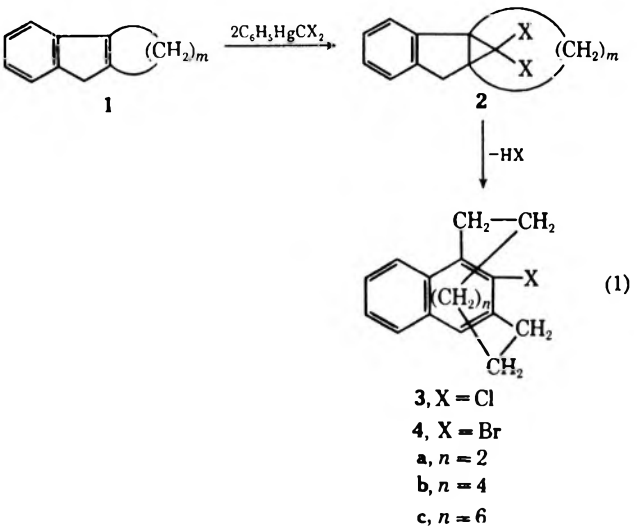
Received January 19, 1970

12,13-Benzo-10-bromo[10]metacyclophane (**4c**) has been prepared and chemical transformations of the derived Grignard reagent (**5a**) and the corresponding aryllithium reagent (**5b**) are described. The Grignard function in **5a** is quite hindered, but reacts normally with mineral acids, deuterium oxide, and benzaldehyde; however, reduction occurs with acetone-d_6, acetaldehyde, and presumably with other enolizable ketones. Reaction of the Grignard reagent **5a** with carbon dioxide is quite slow, and, with oxygen, transannular reactions occur. The ultraviolet spectrum of ketones **8** and **9** suggests that lack of coplanarity of carbonyl group with the aromatic ring results in considerable change in wavelength of absorption.

We have recently[2,4] described synthesis of the 1,3-bridged naphthalenes **3a–3c** and **4a** by procedures summarized in eq 1. The lower practical limit of m (in **1**)

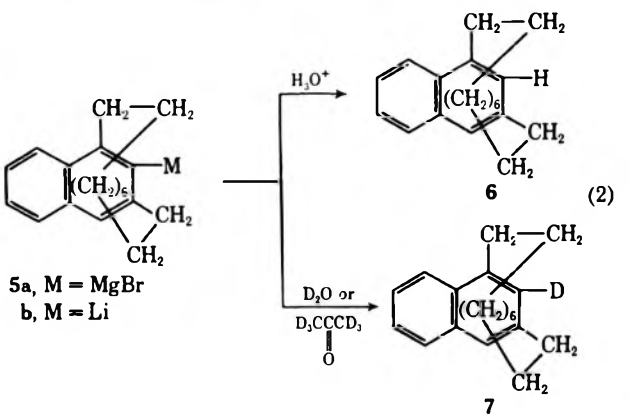


(1)

in this synthesis was found to be six, and the aromatic ring containing the methylene bridge in **3a** and **4a** was observed to be highly strained and reactive. The present work was directed to a study of the chemical behavior of the analogous 1,3-bridged aromatic system, 12,13-benzo-16-bromo[10]metacyclophane (**4c**).

Preparation of 4c.—12,13-Benzo-16-bromo[10]metacyclophane (**4c**) was prepared in 80% yield by reaction of **1** (m = 10) with two equivalents of potassium *t*-butoxide and bromoform, essentially as previously described for the preparation of **3c**.[2] The nmr spectrum of **4c**, which showed characteristic broad and complex methylene absorption at τ 6.00–10.27 and which was analogous to that reported for **3c**, established the fact that the methylene bridge is tightly packed over the face of the aromatic system to which it is attached and that the methylene bridge cannot pass over the halogen to the other face of the aromatic system (*i.e.*, the molecule is asymmetric and exists as a *dl* pair).[2] The very high field absorption of **4c** near τ 10.27 was expected by analogy with **3a**[2] (near τ 11.0) since the bridging atoms are held closely over the face of the benzene ring, and, as a consequence, are held closely in the shielding cone of the aromatic ring. The metacyclophane **4c** reacted readily with magnesium in tetrahydrofuran to give the corresponding Grignard reagent **5a** or with *n*-butyllithium in hexane to give the corresponding aryllithium derivative **5b**. By contrast, the analog **3c** did not react[4] with magnesium even when an entrainment agent was added.

Reactions of 5. A. With Acids.—The Grignard reagent **5a** reacted in a normal manner with dilute hydrochloric acid to give **6** in quantitative yield and with D_2O to give **7** in 74% yield (75% deuterium incorporation by nmr). When the Grignard reagent **5a** reacted with acetone-d_6 the metacyclophane **7** was obtained (85% yield, 70% deuterium incorporation) together with only trace amounts of other materials which could have been addition products. Similarly, the reaction of **5b** with mineral acid gave **6** in 99% yield.



(2)

The nmr spectrum of **6** is in sharp contrast to that of the bromo derivative **4c**. The rather simple spectrum for the former (see Experimental Section) shows that conformational averaging is occurring and that the bridge methylenes pass rapidly to the opposite face of the aromatic ring.

The position of deuterium in **7** was evident by its nmr spectrum, which showed almost complete disappearance of hydrogen in the aromatic region at τ 2.76. This absorption for the hydrogen at position 16 in **6** corresponds to absorption at τ 3.06 for the 2-hydrogen in 1,3-dimethylnaphthalene[4] which is also upfield, and which similarily exhibits no *ortho* coupling as predicted for the 1,3-dialkylnaphthalene structure.

B. With Benzaldehyde and with Acetaldehyde.—It was of interest to note that reaction of **5a** with excess benzaldehyde proceeded directly to the ketone **8** (63% yield). Although oxidation of magnesium salts of alcohols by hydride transfer wth aldehydes is well

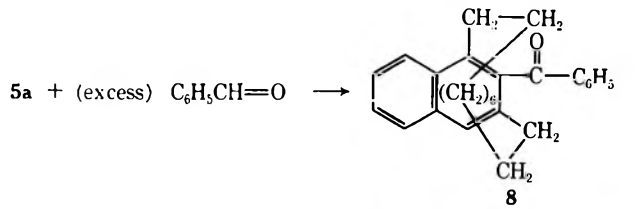
(1) Supported by the National Science Foundation, Grants GP-6169X and GP-11918.

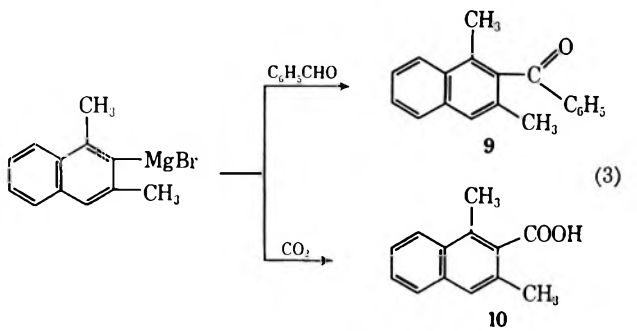
(2) For the preceding article in this series, see W. E. Parham, D. R. Johnson, C. T. Hughes, M. K. Meilahn, and J. K. Rinehart, *J. Org. Chem.*, **35**, 1048 (1970).

(3) Taken in large part from the thesis of Richard W. Davenport, The University of Minnesota, 1969.

(4) W. E. Parham and J. K. Rinehart, *J. Amer. Chem. Soc.*, **89**, 5668 (1967).

known, the ketone **8** rather than the corresponding alcohol was unexpected in view of the steric demands in this system.





Rekker and Nauta[5] have investigated steric effects in the ultraviolet spectrum of substituted benzophenones, and have shown that *ortho* substituents prevent coplanarity of the carbonyl group with the benzene nuclei. These steric effects cause only small changes in the wavelength and somewhat larger decreases in the absorption intensity. By analogy, the uv spectrum of **8** [λ_{max} 232 mμ (ϵ 66,100), 250 (sh) (22,600), 276 (sh) (8240) and 320 (sh) (595)] was expected to be similar to that of 2-benzoylnaphthalene[6] [λ_{max} 254 mμ (31,600), 285 (11,500), and 335 (2400)]. In view of the great difference noted, 2-benzoyl-1,3-dimethylnaphthalene (**9**) was prepared (eq 3) as a model. The uv spectrum of **9** (see Experimental Section) was in good agreement with that of **8**. The *ortho* substituents in both of these ketones undoubtedly prevent coplanarity of the naphthalene ring and the carbonyl groups, and unlike previous reports for related hindered benzophenones, lack of coplanarity of the carbonyl group with the aromatic ring results in considerable change in wavelength of absorption.

There was no evidence for the formation of addition products when **5a** was treated with acetaldehyde; extensive enolization occurred, as evidenced by the isolation of **6** (64% yield).

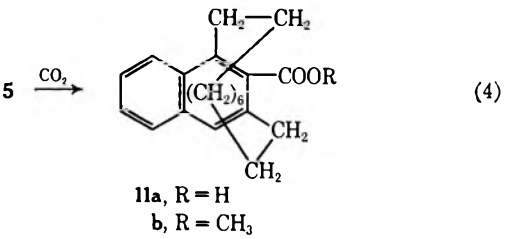
These results, coupled with those described for reaction of **5a** with acetone-d_6, established that functionality at C-16 in **5** could be introduced by organometallic addition reactions to carbonyl groups provided that no enolizable hydrogen was present in the carbonyl function.

C. With Carbon Dioxide.—Reaction of **5a** with crushed Dry Ice, under conditions which gave excellent yields (73%) of the model compound **10**, gave only the metacyclophane **6** (96%). While the result was surprising, the Grignard reagent is highly hindered and prefers to react with water, inevitably present on Dry Ice, rather than carbon dioxide, even though the latter is present in large excess.

(5) R. F. Rekker and W. Th. Nauta, *Rec. Trav. Chim. Pays-Bas*, **73**, 969 (1954); *Spectrochim. Acta*, **8**, 348 (1957).

(6) L. Láng, "Absorption Spectra in the Ultraviolet and Visible Region," Academic Press, New York, N. Y., 1961.

In one experiment the acid **11a** was obtained from **5a** in 48% yield, together with **6** (20%) and an unidentified

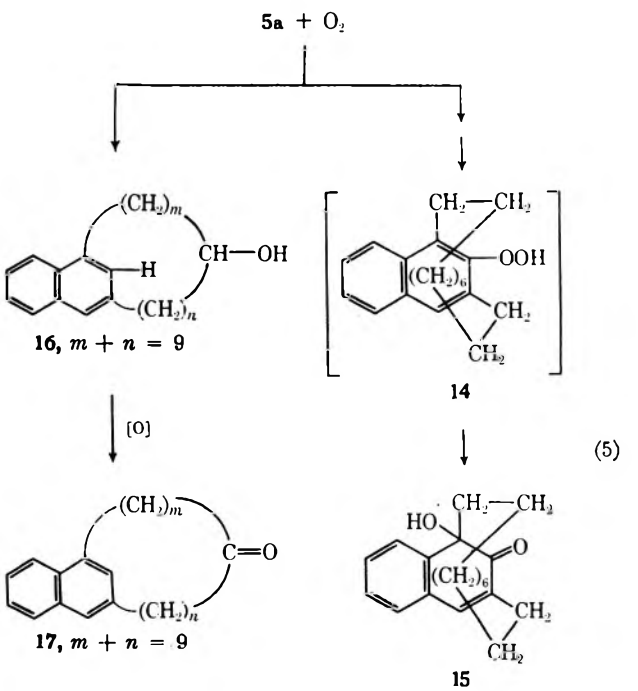


hydrocarbon (see Experimental Section), by bubbling dry carbon dioxide (generated from Dry Ice) through the Grignard reagent for 6 hr. The ester **11b** was prepared from the acid **11a**; however, preparation of the acid by this procedure could not be repeated. The major products from such reactions were subsequently shown to be **6** (~22%), **15** (~18%), and **16** (~42%). Attempts to prepare the acid **11a** from **5a** using >99% pure commercial carbon dioxide were generally unsuccessful.

Reaction of the lithium reagent **5b** with solid Dry Ice also gave **6** (89% yield); however, reaction of **5b** with carbon dioxide generated from Dry Ice gave the acid **11a** in 18% yield, or with high purity commercial carbon dioxide the acid **11a** in 38% yield. These results were reproducible.

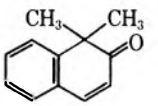
D. With Oxygen.—In a number of reactions of the type described in section C, the Grignard reagent was completely reacted but only small quantities of **6** or acid **11a** were formed. It was concluded that the Girgnard reagent **5a** was reacting selectively with small concentrations of oxygen present as an impurity in the carbon dioxide. This conclusion was confirmed by a study of the reaction of **5a** with oxygen.

Oxygen was bubbled through a solution of the Grignard reagent in tetrahydrofuran for 2 hr (tlc analysis indicated the reaction was complete within 30 min). The products isolated and characterized were the metacyclophane **6** (42%), the α-hydroxy ketone **15** (16%), and a mixture of isomeric alcohols **16** (34%) formed by transannular reaction (eq 5). These results compare



with yield of 22%, 18%, and 42% **6**, **15**, and **16**, respectively, when the Grignard reagent **5a** was treated with carbon dioxide generated from Dry Ice.

The structure of the hydroxy ketone **15** was not established unequivocally, but was assigned on the basis of its composition; comparison of its ultraviolet spectrum with that of **18**;[7] its infrared spectrum which showed strongly hydrogen bonded OH at 3520 cm^{-1}



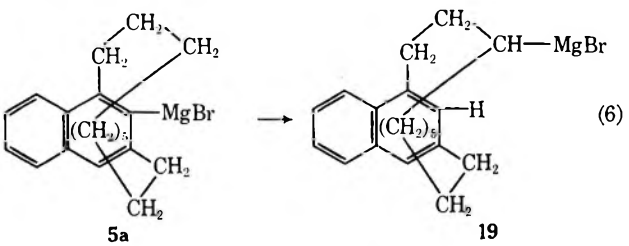
18

characteristic of α-hydroxy ketones;[8] and its nmr spectrum.[9] The hydroxy ketone **15** is assumed to be derived from the expected hydroperoxide **14** (eq 5) and, while arylhydroperoxides do not normally lead to such products, the effective rearrangement of **14** to **15** is logical for such a strained system.[10]

The mixture of alcohols **16** was obtained as an oil that was partially crystallized to give one pure isomer of **16** (11% overall yield from **5a**). The ir and nmr spectra of the mixture of alcohols were essentially identical with those of the pure isomer, which suggested that the mixture contained only isomers of **16**. The alcohols could not be resolved by tlc; however, oxidation of the mixture with Jones reagent gave a mixture of ketones in 79% yield which showed four spots on tlc. The ir and nmr spectra of this mixture suggested that only isomers of the ketone **17** (eq 5) were present. The principal isomeric ketone was isolated in 26% yield from the isomeric alcohols and in 89% yield from the pure isomer of **16**. From these data it was concluded that the alcohols **16** consisted of at least four isomers (the OH groups at different positions on the methylene bridge) one of which comprised a minimum of 55% of the mixture.

The uv spectrum of the major ketone **17** derived from the major alcohol **16** showed typical naphthalene absorption similar to the metacyclophane **6**. The nmr spectrum of this ketone showed for the methylene protons τ 6.42–6.68 (2 protons), 6.88–7.38 (4 protons), and 7.88–9.55 (12 protons). Using the data of Tiers[11] and standard chemical shifts it was concluded that only when the carbonyl group is at C_3 or C_8 (C_1, C_2, C_9, and C_{10} being eliminated by the nmr spectrum of the major alcohol **16**) on the chain will there be six protons absorbing in the region of τ 6.4–7.6 as experimentally observed. Thus, it was concluded that the major transannular alcohol derived by reaction of **5a** with oxygen has the hydroxyl function at either C_3 or C_8 of the methylene chain. This conclusion is consistent with examination of models which show hydrogen at C-3 and C-8 in close proximity to functionality at C-16.

The mechanism of the transannular reaction of **5a** leading to **16** is not known. It does not appear that the Grignard reagent undergoes appreciable exchange in the absence of oxygen as shown in **5a** → **19** (eq 6), since the Grignard reagent behaves normally in its reactions with acids and acetone-d_6. The details of the mechanism are under further examination and will be reported subsequently.



5a **19** (6)

Experimental Section

Glpc separations were performed on a Beckman Model GC-4 or Varian-Aerograph Model 90-P instrument. All ultraviolet spectra were determined in 95% ethanol. Petroleum ether used, unless otherwise specified, had bp 60–70°.

12,13-Benzo-16-bromo[10]metacyclophane (4).—Decahydrocyclododec[*b*]indene (0.0532 mol) was treated with bromoform (0.106 mol) and potassium *t*-butoxide (0.256 mol) in anhydrous benzene (200 ml, 20 min at 0°) by a procedure similar to that described[2,4] for related syntheses with chloroform. Chromatography (alumina, petroleum ether as eluent) of the oil gave 0.0426 mol (80.1% yield) of **4c** (mp 57–63.5°) which was purified (from ethanol) to give pure **4c**: mp 63–64.5°; uv max 232 mμ (sh) (ϵ 68,800), 237 (77,300), 268 (sh) (3960), 278 (5280), 287 (5650), 298 (sh) (3960), and 320 (339); nmr (CCl_4) τ 1.90–2.76 (m, 4.8, aromatic H) and 6.00–10.27 (very complex, 20.2, CH_2); mass spectrum *m/e* 344 (calcd 344).

Anal. Calcd for $C_{20}H_{25}Br$: C, 69.56; H, 7.30. Found: C, 69.56; H, 7.33.

12,13-Benzo[10]metacyclophane (6). 1. From 5a.—A mixture of **4c** (0.273 g, 0.792 mol) and magnesium (0.108 g, 0.00444 g-atom) was heated at the reflux temperature under nitrogen for 4 hr after which time glpc analysis (6 ft, 1/8 in., 20% SE-30 on AW-DMCS, 200°) showed that all **4c** was consumed. The cooled mixture was hydrolyzed with aqueous hydrochloric acid (10%, 10 ml), the resulting mixture was extracted with ether, and the ether was dried ($MgSO_4$). The oil (0.202 g, 96% yield) obtained by concentration of the ether was shown to be ~100% pure **6** by glpc analysis using *n*-docosane as an internal standard. Pure **6** was obtained as a solid, mp 38–39°, by recrystallization of the oil from petroleum ether, bp 30–60°, at −78°, and showed uv max 225 mμ (sh) (ϵ 60,600), 231 (85,200), 278 (sh) (5290), 285 (5650), 293 (sh) (4440), and 322 (363); nmr (CCl_4) τ 1.96–2.72 (m, 5.0, aromatic H), 2.76 (d, 0.9, J = 2 Hz, H at C_{16}), 6.91 (t, 2.0, J = 7.0 Hz, benzylic CH_2), 7.20 (t, 1.9, J = 7.0 Hz, benzylic CH_2), and 7.97–9.33 (m, 16.2, CH_2); mass spectrum *m/e* 266 (calcd 266).

Anal. Calcd for $C_{20}H_{26}$: C, 90.16; H, 9.84. Found: C, 90.29; H, 9.96.

2. From 5b.—A solution of **4c** (0.565 g, 1.64 mmol) in anhydrous hexane (10 ml) was added over a period of 10 min to a solution of *n*-butyllithium (3.3 ml of 1.5 m *n*-butyllithium in hexane, 4.9 mmol, threefold excess) in anhydrous hexane (5 ml) maintained under a nitrogen atmosphere. The mixture was heated at reflux for 5.5 hr when glpc (see 1, above) showed complete absence of **4c**. The mixture was treated as in 1, above, to give 0.396 g (91%, 98% corrected for amount used for analysis) of pure **6**.

12,13-Benzo[10]metacyclophane-16-*d* (7). 1. From 4c.—The procedure was essential as described for **6** from **4c** except that 3 drops of 1,2-dibromoethane was added as a carrier and an 8-hr reflux period was required for complete reaction of **4c**. The mixture was treated with deuterium oxide (1 ml) stirred over-

(7) R. D. Campbell and N. H. Cromwell, *J. Amer. Chem. Soc.*, **79**, 3456 (1957).

(8) L. Joris and P. von R. Schleyer, *ibid.*, **90**, 4599 (1968).

(9) The nmr spectrum is summarized in the Experimental Section. The allylic protons in **15** are nonequivalent owing to the asymmetric center at C_5: one of the allylic protons is deshielded by the adjacent carbonyl group; consequently, the allylic protons have widely different chemical shifts.

(10) The conversion of one aromatic ring carbon atom from sp^2 to sp^3 relieves strain. The enhanced reactivity of strained systems of this type toward electrophilic reagents has already been noted and discussed in ref 2. Rather obvious reaction paths from the conversion of **14** to **15** can be formulated.

(11) G. V. D. Tiers, "Characteristic Nuclear Magnetic Resonance (NMR) 'Shielding Values' (Spectral Positions) for Hydrogen in Organic Structures," Minnesota Mining and Manufacturing Company, St. Paul, Minnesota, 1958. This assignment is tentative since the data of Tiers are gathered from saturated acyclic systems and may not be applicable to **17**. For example, this treatment ignores possible transannular shielding or deshielding effects which possibly could be important in this system.

night and then treated with aqueous acid and processed as above. The oil was chromatographed on alumina (Woelm neutral, activity I, 20 g, petroleum ether was used as eluent). The cyclophane **7** was obtained pure (by glpc) as an oil (74% yield) that was recrystallized to mp 38.5–39.5°. The infrared spectrum of **7** was essentially identical with that of **6** but absorption at 772 cm^{-1} was considerably less intense. Pure **7** showed uv max 225 mμ (sh) (ε 61,700), 231 (93,400), 276 (sh) (5410), 286 (5630), 292 (sh) (4720), and 323 (412); nmr (CCl_4) τ 1.96–2.79 (m, 5.25, indicating 75% deuterium incorporation, aromatic H), 6.91 (t, 2.0, J = 7.0 Hz, benzylic CH_2), 7.20 (t, 2.0, J = 7.0 Hz, benzylic CH_2), and 7.97–9.33 (m, 17.3, CH_2).

2. **From Acetone-d_6.**—The procedure was essentially the same as that described above. Acetone-d_6 (1 g, Stohler Isotope Chemical Co.) was added and the mixture was stirred at room temperature overnight prior to processing. The resulting oil was purified by preparative tlc (alumina PF 254, petroleum ether). Two bands (R_f 0.8 and 0.0) were separated and eluted with chloroform. The deuterated cyclophane **7** (R_f = 0.8) solidified (mp 36–38.5°, 84.5% yield) and was further purified by recrystallization (petroleum ether, bp 30–60°, at −78°) to mp 38.5–39.5° and was identical with **7** prepared above, mass spectrum analyses indicated 70% deuterium incorporation.

The other band (R_f 0.0) was shown by tlc (silica gel HF 254, benzene) to contain at least six components and was not further processed.

12,13-Benzo-16-benzoyl[10]metacyclophane (8).—A mixture containing **4c** (0.620 g, 1.80 mmol), magnesium (0.120 g, 0.00494 g-atom), and 1,2-dibromoethane (4 drops) in tetrahydrofuran was heated at reflux for 6 hr [until **4c** completely reacted (by tlc)] and freshly distilled benzaldehyde (0.912 g, 8.6 mmol) was added all at once. The resulting stirred mixture was allowed to cool to room temperature and was then stirred overnight and finally for 2 hr at the reflux temperature. The dry oil obtained by processing the mixture in a conventional manner was chromatographed on alumina (40 g, petroleum ether). There was obtained cyclophane **6** (25.2% yield) and the ketone **8** as an oil (0.422 g, 64% yield) which melted at 78.5–84° after crystallization from ethanol–water. The solid ketone was rechromatographed and the product was recrystallized from acetone–water to give pure **8**: mp 85.5–88.5°; uv max 232 mμ (ε 66,100), 250 (sh) (22600), 276 (sh) (8240), and 320 (sh) (595); ir (KBr) 1665 cm^{-1} (C=O), 743 and 698 (*ortho* and monosubstituted benzene); ir (CCl_4) 1678 cm^{-1} (C=O); nmr (CCl_4) τ 1.88–3.00 (m, 9.9, aromatic H) and 6.38–10.47 (complex, 20.1, CH_2).

Anal. Calcd for $C_{27}H_{30}O$: C, 87.52; H, 8.16. Found: C, 87.43; H, 8.18.

2-Bromo-1,3-dimethylnaphthalene was prepared from 2,3-dimethylindene[4] essentially as described for **4c**. The crude material was chromatographed on alumina (petroleum ether) and was obtained as a liquid: bp 92–93° (0.10 mm); 75% yield; $n^{25}D$ 1.6494; uv max 232 mμ (log ε 4.93), 245 (sh) (3.44), 266 (sh) (3.60), 275 (3.73), 285 (3.76), 296 (3.58), 319 (sh) (2.37), 324 (sh) (2.37); nmr (CCl_4) τ 2.18–2.93 (m, 5, aromatic H), 7.42 (s, 3, CH_3), 7.61 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{11}Br$: C, 61.30; H, 4.72, Br, 33.99. Found: C, 61.52; H, 4.75; Br, 33.78.

2-Benzoyl-1,3-dimethylnaphthalene (9) was prepared from the Grignard reagent obtained from 2-bromo-1,3-dimethylnaphthalene and benzaldehyde by a procedure similar to that described above for **8**. The crude ketone was obtained by chromatography as a yellow oil (13.2% yield) that solidified, mp 101.5–106.5° (one spot by tlc on alumina HF 254, petroleum ether, R_f 0.15). Recrystallization of the crude ketone from ethanol gave pure **9**: mp 109.5–110.5°; uv max 227 mμ (ε 74,700), 250 (21,000), 280 (sh) (7800), 292 (sh) (5380), and 320 (sh) (742); ir (CCl_4) 1774 cm^{-1} (C=O); nmr ($CDCl_3$) τ 1.67–2.87 (m, 10.3, aromatic H), 7.53 (s, 2.9, CH_3), and 7.73 (s, 2.8, CH_3).

Anal. Calcd for $C_{19}H_{16}O$: C, 87.68; H, 6.17. Found: C, 87.86; H, 6.05.

1,3-Dimethyl-2-naphthoic Acid (10).—The Grignard reagent was prepared under a nitrogen atmosphere from 2-bromo-1,3-dimethylnaphthalene (10.6 g, 0.045 mol) in anhydrous ether, magnesium (1.20 g, 0.0494 g-atom) and 1,2-dibromoethane (5 drops). The reagent was added to a slurry of Dry Ice in ether. The resulting mixture was treated with 20% sulfuric acid (20 ml), and the resulting mixture was extracted with ether. The crude acid **10** (7.23 g, 72.6% yield) was obtained from the dry ether ($MgSO_4$) extract. The pure acid (5.62 g, 62.3% yield, mp 147.5–148.5° from toluene), showed uv max 227 mμ (ε 66,400), 274 (sh) (5230), 280 (5610), 290 (sh) (4250), 307 (sh) (697), 315 (sh) (557), and 321 (583); ir (Nujol) 3250–2200 cm^{-1} (OH) and 1700 (C=O); nmr ($CDCl_3$) τ −0.20 (broad s, 1.2, –OH), 1.83–2.81 (m, 5.1, aromatic H), 7.23 (s, 2.8, 1 CH_3) and 7.43 (s, 3.0, 3-CH_3).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.98; H, 6.15.

Methyl 1,3-dimethyl-2-naphthoate (from 10 and diazomethane) showed mp 51–52° (from methanol–water); uv max 227 mμ (ε 69,600), 272 (5020), 281 (5540), 293 (sh) (4060), and 323 (753); ir (Nujol) 1732 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.26; H, 6.81.

12,13-Benzo-16-carboxy[10]metacyclophane (11a).—The Grignard reagent was prepared as described for the preparation of **6** [1,2-dibromoethane was used as a carrier and about 6 hr was generally required for complete conversion (glpc) of **4c**]. The Grignard reagent was treated as follows.

(a) **With Crushed Dry Ice.**—Such reaction gave only the reduced cyclophane **6** (~96% yield).

(b) **With Carbon Dioxide Generated from Dry Ice.**—In these experiments the carbon dioxide was dried by passing successively through columns (2 ft × 1.5 in.) of calcium chloride Tel-Tale® (a silica gel desiccant, Davison Chemical Co.) and molecular sieves (Linde 13X) and then bubbled through the Grignard mixture for 6 hr. Chromatography of the mixture of products obtained by conventional means on silica gel using petroleum ether–acetone as eluent gave (1) reduced metacyclophane **6** (0.092 g, 19.8% yield), (2) a hydrocarbon (0.07 g crude, mp 113–140°, petroleum ether–2% acetone), and (3) the acid **11a** (0.26 g, 48% yield, mp 213–214°, petroleum ether–10% acetone). Attempts to repeat this experiment failed.

The **unknown hydrocarbon** showed mp 147–149° (from acetone); uv max 231 mμ ($\epsilon^{1\%}_{1cm}$ 2620), 237 (sh) (1550), 276 (sh) (173), 287 (205), 298 (sh) (153), and 322 (12.8); nmr (CCl_4) τ 2.00–3.00 (m, aromatic H), and 6.07–9.76 (complex, CH_2), CH_2/aromatic = 3.96; mass spectrum m/e (rel intensity) 264 (16), 282 (100), 566 (1.8).

Anal. Found: C, 89.98; H, 9.90.

Acid 11a showed mp 213.5–215.5° (from ethanol–water); uv max 234 mμ (ε 81,300), 286 (5210), and 325 (511); ir (KBr) 3600–2150 cm^{-1} (OH), 1678 (C=O), 1455 and 1440 (CH_2), 1286 and 1262 (aryl C=O stretch), and 750 (*ortho* substituted benzene); nmr ($CDCl_3$) τ 0.47 (broad s, 0.9–COOH), 1.67–2.67 (m, 5.0, aromatic H) and 6.06–10.50 (very complex, 21.0 CH_2).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.43; H, 8.55.

The methyl ester 11b (from 11a and diazomethane) showed mp 112.0–113.0° (from methanol–water); uv max 233 mμ (ε 67,300), 283 (5210), and 325 (635); ir (KBr) 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.49; H, 8.99.

(c) **Isolation of 15 and 16.**—An experiment using **4c** (2.00 g, 5.80 mmol) was conducted essentially as described in (b), above, except the carbon dioxide was pretreated through columns of only calcium chloride and molecular seives (Linde 4A). The crude product obtained subsequent to neutralization with sulfuric acid and extraction with chloroform, was chromatographed over silica gel (50 g). Elution of the column with petroleum ether gave **6** (0.334 g, 21.6% yield). The next fraction (0.112 g), eluted with petroleum ether–2% acetone, contained at least four components (tlc) and was not processed further.

The α-hydroxy ketone 15 (0.303 g, 17.5%, eluted with petroleum ether −4% acetone) showed one spot (R_f 0.50) on tlc (silica gel HF 254, petroleum ether–10% acetone–1% acetic acid) and showed the following: mp 143–144.5° (from ethanol–water); uv max 242 mμ (ε 15,900) and 317 (9500); ir (CCl_4) 3520 cm^{-1} (OH), 1671 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.27–3.07 (m, 5.2, aromatic H and C=C—H), 6.23 (s, 0.9, OH), 6.80–7.30 (m, 1.1, allylic H), 7.63–9.67 (m, 18.8, allylic H and CH_2); mass spectrum m/e 298 (calcd mol wt 298).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.44; H, 8.96.

The alcohols 16 (0.690 g, 42.4% yield, eluted with petroleum ether–6% acetone) showed only one spot on tlc (silica gel HF 254, petroleum ether (bp 60–70°)–20% acetone–1% acetic acid, R_f = 0.35). The isomeric alcohols **16** were dissolved in petroleum ether and allowed to stand at −20° for several days. The principal isomeric alcohol **16** crystallized and showed mp 114–115°; uv max 225 mμ (sh) (ε 64,600), 231 (96,100), 278 (sh) (5570),

285 (4890), 292 (sh) (4820), 308 (sh) (751), and 322 (455); ir (Nujol) 3415 cm^{-1} (broad OH) and 735 (*ortho* substituted benzene); nmr ($CDCl_3$) τ 1.93–2.96 (m, 5.8, aromatic H), 6.36–7.43 (m, 4.9, benzylic CH_2 and -CHOH), and 7.77–9.53 (m, 15.3, CH_2 and OH); mass spectrum *m/e* 282 (calcd mol wt 282).

Anal. Calcd for $C_{20}H_{26}O$: C, 85.06; H, 9.28. Found: C, 85.03; H, 9.37.

The spectra of the crude alcohol and the isolated pure isomeric alcohol were essentially identical and suggested that the former contained only isomers of **16**.

The hydroxy ketone **15**, the alcohols **16** and acid **11a** (~10%) were obtained when commercial carbon dioxide (99.8%, J. T. Baker Chemical Co.) was employed.

Preferred Procedure for 11a.—The acid **11a** (mp 202–208°, 38% yield) was prepared reproducible from the aryl lithium derivative prepared from **4c** (1.00 g, 2.90 mmol), *n*-butyllithium (10 ml, 1.5 *M* in hexane, ~15 mmol) in anhydrous hexane (50 ml) at reflux (~6 hr until tlc confirmed the absence of **4c**). The solution was cooled to −78° and carbon dioxide (99.8%, J. T. Baker Chemical Co.) was passed over the surface for 3.5 hr. The mixture was allowed to warm to room temperature and carbon dioxide was passed through the solution for 41 hr. The acid **11a** is not soluble in alkali. Water was added to the mixture which was then extracted with chloroform (white solid that separated was kept in solution by addition of more chloroform). The combined organic layer was washed with water. The oil obtained from the dried ($MgSO_4$) extract partially solidified. The mixture was triturated with cold (0°) petroleum ether to give acid **11a** (0.340 g, 38% yield; mp 202–208°, mp 213.5–214° from ethanol–water).

Reactions of 5a with Oxygen.—The Grignard reagent **5a**, prepared from **4c** (0.500 g, 1.45 mmol) as described above, in tetrahydrofuran (50 ml) was cooled to room temperature and oxygen (Air Reduction Co.), dried by passing through a column of $CaCl_2$, was bubbled through the mixture for 2 hr. Analysis (tlc, silica gel HF 254, petroleum ether–10% acetone) showed alcohol **16** (R_f 0.16), hydroxy ketone **15** (R_f 0.44), and reduced cyclophane (R_f 0.78). The crude mixture obtained subsequent to hydrolysis (H_2SO_4, 15%, 10 ml, 20 min), extraction (ether, 15 ml), washing (H_2O), and drying ($MgSO_4$) was purified by preparative tlc (silica gel PF 254, petroleum ether–10% acetone). The products (yields) were reduced cyclophane **6** (~42% yield), unchanged **4c** (~18%), unidentified mixture (0.04 g), hydroxyketone **15** (0.06 g, 15% yield; mp 125–131°, mp 142–143° from ethanol–water), and alcohols **16** (0.130 g, 34.4%).

In a duplicate experiment the yield of **15** was 9% and the yield of **16** was 37%.

Oxidation of 16. (a)—The pure isomer of **16** (0.180 g, 0.639 mmol, mp 111.5–113.0°) in reagent grade acetone was oxidized with Jones reagent[12] (0.7 ml of 1 *M* solution prepared from 35 g of chromic acid, 250 ml of water and 30.5 ml of concentrated sulfuric acid) added dropwise over a period of 5 min. Analysis of the crude white ketone (mp 122–125°, 0.160 g, 89.5% yield) by tlc (silica gel HF 254, petroleum ether–5% ethyl acetate) indicated that a single product (R_f 0.38) was present. The pure ketone showed mp 125–126° (from ethanol); uv max 230 mμ (ε 77,800), 277 (sh) (5590), 282 (6000), 291 (sh) (4840), 308 (sh) (698) and 323 (652); ir (Nujol) 1708 cm^{-1} (C=O); nmr ($CDCl_3$) τ 1.77–3.15 (m, 5.9, aromatic H) and 6.42–9.55 (m, 18.1, CH_2); the methylene protons (τ 6.42–9.55) consisted of a series of multiplets with principal absorption as follows, 6.42–6.68 (1.8), 6.88–7.38 (3.7), and 7.88–9.55 (11.7); mass spectrum *m/e* 280 (calcd mol wt 280).

Anal. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63. Found: C, 85.82; H, 8.76.

(b)—The oxidation was repeated as described above but using the mixture of isomeric alcohols of **16**. The ir spectrum of the product was essentially identical with the product described in (a), above; the nmr spectrum was quite similar with the exception of a multiplet at τ 6.68–6.88 and a multiplet at 7.90 that are absent in the spectrum of the ketone described above. Recrystallization of this mixture (petroleum ether, bp 30–68° at −20°) gave the principal product (mp 122–123.5°, mixture melting point with ketone in (a), mp 125–126°, was 122–125°). The mother liquor gave a mixture of ketone (mp 64–82°); analysis by tlc (silica gel HF 254, petroleum ether–5% ethyl acetate) suggested that four isomeric ketones were formed by oxidation of **16**.

Registry No.—**4c**, 25097-45-4; **6**, 25097-46-5; **7**, 25097-47-6; **8**, 25097-48-7; **9**, 25097-49-8; **10**, 25097-50-1; **11a**, 25097-51-2; **11b**, 25097-52-3; **15**, 25097-53-4; bromo-1,3-dimethylnaphthalene, 25097-54-5; methyl 1,3-dimethyl-2-napthoate, 25097-55-6.

(12) J. Meinwald, J. Crandall and W. E. Hymans, *Org. Syn.*, **45**, 77 (1965).

Strained-Ring Systems. IX.[1a] The Preparation of Some 5-Substituted Bicyclo[3.1.0]hexane-1-carboxylic Acids

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Several 5-substituted bicyclo[3.1.0]hexane-1-carboxylie acids have been prepared and characterized. Dimethyl bicyclo[3.1.0]hexane-1,5-dicarboxylate (**3**) was prepared by a 1,3 elimination of hydrogen bromide from dimethyl 1-bromocyclohexane-1,3-dicarboxylate (**8**) in 85% yield. From bicyclic diester **3**, by standard reaction sequences, bicyclo[3.1.0]hexane-1,5-dicarboxylic acid (**9**) and 5-carbomethoxy- (**10**), 5-bromo- (**12**), 5-carboxamido- (**14**), and 5-cyanobicyclo[3.1.0]hexane-1-carboxylic acid (**16**) were prepared. Bicyclo[3.1.0]hexane-1-carboxylic acid (**19**) was prepared by a 1,3 elimination of the elements of *p*-toluenesulfonic acid from methyl 3-tosyloxycyclohexane-1-carboxylate (**17**) and subsequent hydrolysis.

Useful methods have been reported for the preparation of bicyclic, bridgehead substituted carboxylic acids.[2–5] This paper presents the syntheses of certain 5-substituted bicyclo[3.1.0]hexane-1-carboxylic acids which were required for pK_a studies as well as solvolytic studies on derivatives of the 1-carbinols.

The key to the synthesis of the bicyclohexanecarboxylic acids was the preparation of dimethyl bicyclo[3.1.0]hexane-1,5-dicarboxylate (**3**). Prinzbach, *et al.*,[6] have reported the synthesis of **3** by a photochemical route. We employed some slight modifications to Prinzbach's procedure to allow preparation of larger quantities of material. Irradiation of a sample of di-

(1) (a) For paper VIII in this series, see R. N. McDonald and G. E. Davis, *J. Org. Chem.*, **34**, 1916 (1969). (b) National Defense Education Act Trainee, 1968–1970.

(2) J. D. Roberts, W. T. Moreland, and W. Frazer, *J. Amer. Chem. Soc.*, **75**, 637 (1953).

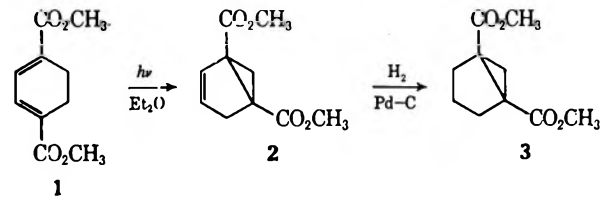
(3) F. W. Baker and L. M. Stock, *J. Org. Chem.*, **32**, 3344 (1967).

(4) C. F. Wilcox and J. S. McIntyre, *ibid.*, **30**, 777 (1965).

(5) C. F. Wilcox and C. Leung, *ibid.*, **33**, 877 (1968).

(6) H. Prinzbach, H. Hagemann, J. Hartenstein, and R. Kitzing, *Chem. Ber.*, **98**, 2201 (1965).

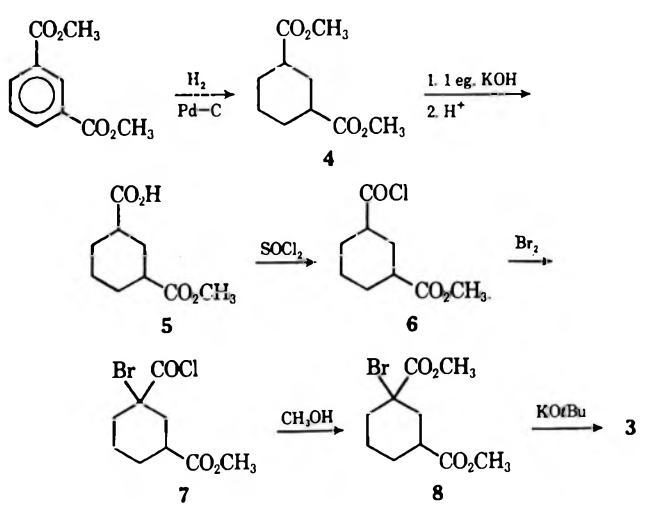
methyl cyclohexa-1,3-diene-1,4-dicarboxylate (1) with a Hanovia Type L, 450-W lamp in ether for 5 hr pro-



duced crude photo diester 2 in 40% yield after distillation. Hydrogenation of 2 over 5% Pd–C produced 3. Analysis of crude 3 by glpc showed the presence of several minor components.

Although 3 was available by this route, considerations of the time involved and small quantities of 3 produced per run suggested that an alternate synthesis of 3 be developed. Using the analogies of Nelson and Mortimer[7] and Wiberg[8] of using an intramolecular anionic displacement reaction in the preparation of [*n*.1.0] systems, a new synthetic route to 3 was devised according to the reaction sequence in Scheme I. Re-

Scheme I



duction of dimethyl isophthalate produced 4 in a *cis*/*trans* ratio of 69:31, as analyzed by glpc. Partial saponification of diester 4, formation of the half-acid chloride 6, α-bromination of 6, and esterification of the product acid chloride 7 produced dimethyl 1-bromocyclohexane-1,3-dicarboxylate (8).

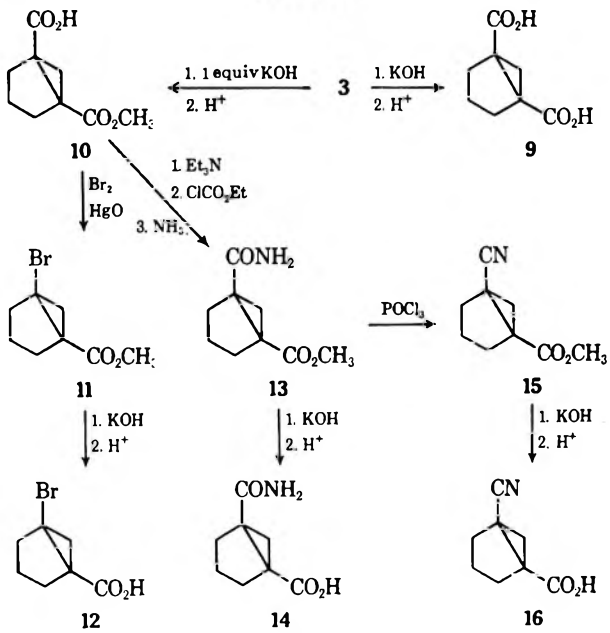
Treatment of 8 with a strong base led to formation of 3 by an intramolecular anionic displacement reaction. Reaction of 8 with sodium hydride in refluxing glyme for 6 hr produced 3 and a mixture of other ester products. Using sodium hydride and refluxing benzene for 24 hr, 3 was produced in crude yield of 50–55%. The nmr spectrum of the distillate also showed small amounts of other ester impurities. However, addition of 1 equiv of potassium *t*-butoxide in *t*-butyl alcohol to 8 in *t*-butyl alcohol produced 3 (85%) in high purity. Diester 3 so obtained was identical in all respects with the diester produced by Prinzbach[6] and represents an independent synthesis and structure proof of this bicyclic diester.

(7) N. A. Nelson and G. A. Mortimer, *J. Org. Chem.*, **22**, 1146 (1957).

(8) K. Wiberg, G. Lampman, R. Ciula, D. Connor, P. Schertler, and J. Lavanish, *Tetrahedron*, **21**, 2749 (1965).

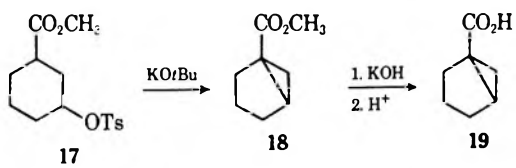
From 3 were produced 5-bromo- (12), 5-cyano- (16), 5-carbomethoxy- (10), 5-carboxamido- (14), and bicyclo[3.1.0]hexane-1,5-dicarboxylic acid (9) by standard routes[2-5] as outlined in Scheme II.

Scheme II



Diester 3 could be saponified completely to diacid 9 or partially to half-ester 10. By a Hundsdiecker reaction 10 was converted to 11 which was hydrolyzed to bromo-acid 12. Half-ester 10 was converted to amide 13 which was then dehydrated to cyano ester 15. Esters 13 and 15 were hydrolyzed to their respective acids, 14 and 16.

Methyl bicyclo[3.1.0]hexane-1-carboxylate (18) was prepared by the method of Nelson and Mortimer[7] with the minor modification of using the *cis* and *trans* tosylate 17 in the 1,3-elimination reaction. Basic hydrolysis of 18 gave bicyclo[3.1.0]hexane-1-carboxylic acid (19).



Experimental Section[9]

Dimethyl Bicyclo[3.1.0]hex-2-ene-1,5-dicarboxylate (2).—The title compound was prepared by a modification of the procedure given by Prinzbach and coworkers.[6] In a usual irradiation apparatus, a solution (degassed with oxygen free nitrogen) of 4.0 g (20.4 mmol) of dimethyl 1,3-cyclohexadiene-1,4-dicarboxylate (1)[10] in 600 ml of anhydrous ether was irradiated for 5 hr. with a Hanovia 450-W lamp (Type L) in a quartz immersion well. The temperature of the solution was kept between −10 and 5° during the irradiation by means of an isopropyl alcohol–Dry Ice bath. It was necessary to wipe the irradiation well clean of polymer

(9) All melting points were determined on a Kofler hot stage and are corrected. Boiling points are uncorrected. Infrared and nmr spectra were obtained on a P-E 137 spectrophotometer and on a Varian A-60 spectrometer. Gas chromatographic analyses were performed using a F & M Model 500, temperature programmed, gas chromatograph. Microanalyses were done by Galbraith Laboratories. Mass spectra were determined on an MS-9 mass spectrometer.

(10) J. Kauer, R. Benson, and G. Parshall, *J. Org. Chem.*, **30**, 1431 (1965).

every 1.5 hr. Concentration of the irradiation solution and subsequent short-path distillation [90–100° (0.005 mm)] of the remaining viscous, yellow oil produced 1.60 g (40%) of crude diester **2**. The ir and nmr spectra were identical with those reported by Prinzbach.[6]

Dimethyl Bicyclo[3.1.0]hexane-1,5-dicarboxylate (3).—In a semimicrohydrogenation apparatus, 3.16 g (16.1 mmol) of crude **2** was hydrogenated in 15 ml of ethanol with 0.3 g of 5% Pd-C and one atmosphere of hydrogen. The reduction product was short-path distilled [65–70° (0.01 mm)] yielding 2.99 g (94%) of a light, colorless liquid. Glpc analysis of the crude mixture on a 10% Carbowax on Chromosorb P column showed at least eight components. The major component (>80%) was collected. Its ir and nmr spectra were identical with those reported for **3**.[6]

Reduction of Dimethyl Isophthalate.—To a solution of 10.0 g (51.6 mmol) of dimethyl isophthalate (Baker Chemical Co.) in 85 ml of dry methanol in a glass liner contained in a 150 ml capacity Magna Dash autoclave was added three spatula tips full of 5% Pd-C catalyst. Hydrogen was pressured into the autoclave to 1600 psi and it was heated to 100° for 48 hr. Pressure loss after cooling was approximately 400 psi. The catalyst was removed by filtration through a thin layer of filter cell and the solvent was removed by flash evaporation. The product from four 10.0-g runs was combined and short-path distilled [85° (0.01 mm)] producing 41.3 g (99.2%) of colorless diester **4**. The ir and nmr spectra agreed with the assigned structures, and the nmr spectrum indicated two different methyl ester singlets corresponding to the *cis* and *trans* isomers.

Separation of the *cis* and *trans* Isomers of Dimethyl Cyclohexane-1,3-dicarboxylate (4).—Glpc analysis of the *cis/trans* mixture reported above on a 8 ft × 0.25 in. 10% Carbowax on Chromosorb P (conditions: column temperature, 215°; helium gas flow, 60 ml/min) gave two peaks with retention times of 3.7 and 4.5 min. Integrations of the peak areas gave relative amounts of approximately 31 and 69%, respectively. Samples of both peaks were collected at a lower column temperature. The product with a retention time of 3.7 min gave an nmr spectrum (CCl_4, TMS internal) exhibiting absorption at τ 6.38 (s, 3, OCH_3), 7.2–7.6 (m, 2), and 7.9–8.5 [m (with characteristic sharp peaks at τ 8.03, 8.13, and 8.93), 8]. The product with a retention time of 4.5 min gave an nmr spectrum (CCl_4, TMS internal) exhibiting absorption at τ 6.40 (s, 3, OCH_3) and 7.6–8.9 [broad multiplet (with characteristic sharp peaks at τ 7.22, 7.92, 8.13, and 8.70), 10]. On the basis of the greater complexity of the multiplet from the ring hydrogens in the nmr spectrum of the second peak relative to the first peak, we have assigned the *trans* configuration to the first peak and the *cis* configuration to the second peak.

Methyl Hydrogen Cyclohexane-1,3-dicarboxylate (5).—To a solution of 39.0 g (0.195 mol) of *cis*- and *trans*-**4** in 50 ml of absolute methanol, 144 ml of a 1.36 *N* potassium hydroxide (0.196 mol) solution in absolute methanol was added dropwise over a 4 hr period. The mixture was heated under reflux for 24 hr and the methanol removed by flash evaporation. The residue was diluted with 100 ml of water and extracted with ether to remove unreacted starting material. The aqueous layer was acidified to pH 2–3 and extracted continuously with ether for 20 hr. The extract was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation leaving a viscous, colorless liquid, crude monoester **5**. Diacid impurity was removed by dissolving crude **5** in carbon tetrachloride and filtering off the insoluble diacid. Monoester **5** was usually not purified further: ir (liquid film) 1720 (broad C=O) and 2500–3400 cm^{-1} (acid OH); nmr (CCl_4, TMS external) τ −1.0 (s, 1, CO_2H), 6.39 (s, 3, OCH_3), and 7.5–8.8 (m, 10, ring protons).

3-Carbomethoxycyclohexane-1-carbonyl Chloride (6).—Crude monoester **5** was dissolved in 30 ml of dry benzene. To this solution was added 40 ml of thionyl chloride and 4 drops of DMF. The mixture was stirred at room temperature for 2 hr and then at 50° for one hr until the evolution of gas had ceased. Solvent and excess thionyl chloride were removed by flash evaporation leaving a yellow liquid which was short-path distilled [80° (0.01 mm)] yielding 28.0 g (70% from 39.0 g of **4**) of colorless acid chloride–ester **6**: ir (thin film) 1730 and 1790 cm^{-1} (C=O); nmr (CCl_4, TMS internal): τ 6.35 (s, 3, OCH_3) and 7.2–8.3 [m (with a characteristic sharp peak at τ 8.31), 10].

Dimethyl 1-Bromocyclohexane-1,3-dicarboxylate (8).—To a solution of 31.0 g (0.152 mol) of acid chloride ester **6** in 30 ml of CCl_4 was added 9.0 ml (0.16 mol) of bromine. The mixture was heated under reflux for 8 hr until evolution of gas had ceased. Solvent and excess bromine were removed by flash evaporation and the yellowish residue was short-path distilled [100° (0.1 mm)] producing 43.0 g of a colorless liquid, crude **7**: ir (thin film) 1810 and 1740 cm^{-1} (C=O); nmr (CCl_4, TMS internal) τ 6.33 (s, 3, OCH_3) and 6.9–8.6 [m, (with characteristic sharp peaks at 7.89, 8.14, and 8.33), 9].

The crude bromination product, **7**, was then added dropwise to 100 ml of dry methanol with stirring at 0°. The solvent was removed after stirring for 1 hr and crystals formed upon standing. After two recrystallizations from methanol–water and sublimation [80° (0.01 mm)], 23.0 g (54% from 31.0 g of **6**) of bromo diester **8** was obtained: mp 73.5–74.5°; ir (KBr) 1725 cm^{-1} (C=O); nmr (CCl_4, TMS internal) τ 6.36 (s, 3, OCH_3), 6.22 (s, 3, OCH_3) and 6.9–8.9 [m (characteristic sharp peaks at 8.05, 8.13, and 8.28), 9]; mass spectrum (70 eV, direct insert) M^+ at *m/e* 278 and 280; mol wt 282 ± 2% (calcd 279.2).[11]

Anal. Calcd for $C_{10}H_{15}O_4Br$: C, 43.03; H, 5.42. Found: C, 42.82; H, 5.38.

Dimethyl Bicyclo[3.1.0]hexane-1,5-dicarboxylate (3) Produced by the 1,3-Elimination Reaction.—To 47.2 g (0.169 mol) of bromo diester **8** dissolved in 200 ml of dry *t*-butyl alcohol was added dropwise a solution of potassium *t*-butoxide in *t*-butyl alcohol [prepared from 7.0 g (0.179 g-atom) of potassium in 200 ml of dry *t*-butyl alcohol] over a 30-min period. During the addition a white precipitate formed and the mixture became thicker as the addition of base was continued. The mixture was allowed to stir 20 min after the addition of base was complete. The precipitate was removed by suction filtration and the filtrate concentrated to a volume of about 60 ml by flash evaporation. More precipitate formed when 200 ml of ether was added to the residue. After removal of precipitate and solvent, the liquid residue was short-path distilled [100° (0.1 mm)] yielding 27.8 g (85.6%) of **3**. Glpc analysis using the same column and conditions used for the analysis of **3** formed by the photochemical route showed only one peak with a retention time the same as that of **3** isolated previously. The ir and nmr spectra of these samples were identical. The mass spectrum (70 eV, heated inlet) showed M^+ at *m/e* 198.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.72; H, 7.15.

Bicyclo[3.1.0]hexane-1,5-dicarboxylic Acid (9).—The title compound was prepared by the procedure given by Prinzbach.[6] Diacid **9** was isolated in 33% yield, sublimed in a sealed melting point tube at 220–225° and decomposed at 236–237° (lit.[6] sublimed 220–230°). The ir and nmr spectra agreed with those reported.[3]

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.74; H, 6.02.

Methyl Hydrogen Bicyclo[3.1.0]hexane-1,5-dicarboxylate (10).—To 39.81 g (0.207 mol) of diester **3** in 100 ml of dry methanol was added dropwise a solution of 12.7 g (0.207 mol) of potassium hydroxide dissolved in 100 ml of dry methanol over a 2-hr period. A slight yellow color formed immediately and remained throughout the reaction. After stirring at room temperature for 24 hr and heating under reflux for an additional 3 hr, the solvent was removed by flash evaporation and crystallization occurred upon standing. To the crystals was added 150 ml of water and unreacted starting material was extracted with three 75-ml portions of ether (6.3 g of **3**). The aqueous layer was acidified to pH 2 and continuously extracted with ether for 24 hr. The extract was dried ($MgSO_4$), concentrated, and the residue was short-path distilled [130–145° (0.005 mm)] yielding 25.0 g (67.8%) of a viscous liquid, crude **10**, which solidified upon standing. From the distillation pot, 1.15 g of diacid was obtained after recrystallizing the residue from ethyl acetate. An analytical sample of **10** was obtained after several recrystallizations from cyclohexane and sublimation: mp 76.0–77.5°; ir (CCl_4) 2500–3500 (acid OH), and 1700 and 1730 (C=O) cm^{-1}; nmr (CCl_4, TMS internal) τ 6.35 (s, 3, OCH_3), 7.3–9.0 [m (with characteristic sharp peaks at τ 7.93, 8.05, 8.75, and 8.84), 8], and −1.1 (s, 1, acid proton); mass spectra (70 eV, heated inlet) M^+ at *m/e* 184.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.67; H, 6.75.

Methyl 5-Bromobicyclo[3.1.0]hexane-1-carboxylate (11).—The procedure for a similar Hunsdiecker reaction was followed.[12]

(11) Molecular weight determined on Mechrolab osmometer, Model 301 A.

(12) J. S. Meek and D. T. Osuga, *Org. Syn.*, **43**, 9 (1963).

A solution of 2.0 g (11 mmol) of half-acid **10** and 1.0 ml (19 mmol) of bromine in 20 ml of bromotrichloromethane (distilled from P_2O_5) was added dropwise over a 2 hr period to a stirred suspension of 1.5 g (7 mmol) of red mercuric oxide in 10 ml of bromotrichloromethane in a flask maintained at 35–40°. Stirring was continued until evolution of gas had ceased. Tlc (silica gel, $CHCl_3$) of the reaction mixture showed two spots, starting material and product. An additional 1.0 g (4.6 mmol) of mercuric oxide was added and evolution of gas increased until the bromine color had disappeared. Tlc showed the reaction to be essentially complete. The mixture was filtered, concentrated by flash evaporation of solvent, diluted with ether, and filtered again. The final filtrate was concentrated and the residue was short-path distilled [70° (0.1 mm)] producing 1.15 g (48%) of **11**: ir (thin film) 1730 (C=O), 1144 (C—O), and 1020 cm^{-1} (cyclopropyl-CH_2); nmr (CCl_4, TMS internal) τ 6.29 (s, 3, OCH_3) and 7.4–8.8 [m (with characteristic sharp peaks at 7.75, 8.07, 8.18, 8.63, and 8.75), 8]; mass spectrum (70 eV, heated inlet) M^+ at *m/e* 218 and 220.

Anal. Calcd for $C_8H_{11}O_2Br$: C, 43.86; H, 5.06. Found: C, 43.75; H, 5.18.

5-Bromobicyclo[3.1.0]hexane 1-carboxylic Acid (12).—A sample of bromoester **11** (1.15 g; 5.25 mmol) was saponified by a similar procedure to that described in the preparation of **9** except that 6.30 meq of base was employed. The crystalline residue from solvent evaporation was recrystallized twice from cyclohexane and sublimed at [80° (0.01 mm)] yielding 0.56 g (52%) of bromo acid **12**: mp 144.5–145.5°; ir (Fluorolube mull) 1700 (C=O), 2500–3200 (acid O—H), and 1048 cm^{-1} (cyclopropyl-CH_2); nmr (CCl_4, TMS internal) τ −2.3 (s, 1, acid proton) and 7.3–8.8 [m (characteristic sharp peaks 7.58, 7.72, 8.03, 8.58, and 8.68), 8].

Anal. Calcd for $C_7H_9O_2Br$: C, 41.00; H, 4.42. Found: C, 41.16; H, 4.42.

Methyl 5-Carboxamidobicyclo[3.1.0]hexane-1-carboxylate (13).—A solution of 5.00 g (27.4 mmol) of half-ester **10** and 2.7 g (28 mmol) of triethylamine in 50 ml of chloroform was cooled in an ice bath and 2.98 g (28 mmol) of ethylchloroformate was added rapidly with stirring. After 15 min anhydrous ammonia was bubbled through the mixture for 1.5 hr. The mixture was allowed to stand for 2 hr, filtered, and removal of the solvent left a yellowish oil. The residue was eluted fairly rapidly through 60 g of alumina (neutral, activity II) with chloroform until tlc (silica gel) showed that the product had ceased coming off the column. The eluant was concentrated and the residue crystallized upon standing. The crude amide ester **13** was recrystallized from a mixture of benzene–hexane yielding 4.1 g (82%) of white, crystalline **13**: mp 85.0–86.5°; ir (Fluorolube mull) 3300 and 3120 (N—H), 1720 (ester C=O), and 1660 cm^{-1} (amide C=O); nmr (CCl_4, TMS internal) τ 3.4–3.7 (m, 2, NH_2), 6.35 (s, 3, OCH_3), and 7.5–8.9 [m (characteristic sharp peaks at 7.95, 8.12, 8.22, 8.78, and 8.87), 8]; mass spectrum (70 eV, direct insert) M^+ at *m/e* 183.

Anal. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15. Found: C, 59.15; H, 7.08.

5-Carboxamidobicyclo[3.1.0]hexane-1-carboxylic Acid (14).—The ester function of **13** was hydrolyzed in the usual manner as described in the preparation of **12**. Crude **14** was recrystallized from 1-propanol–ether yielding 0.49 g (53% from 1.0 g of **13**) of white, crystalline **14**. Amide acid **14** was further purified by sublimation [160° (0.1 mm)], another recrystallization, and resublimation: mp 189.0–190.5°; ir (Fluorolube mull) 3200 and 3300 (N—H), 2200–3000 (acid O—H), 1725 (acid C=O), 1640 (amide C=O), and 1045 cm^{-1} (cyclopropyl CH_2).

Anal. Calcd for $C_8H_{11}O_3N$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.70; H, 6.48; N, 8.23.

Methyl 5-Cyanobicyclo[3.1.0]hexane-1-carboxylate (15).—A solution of 1.0 g (5.52 mmol) of amide ester **13**, 1.5 ml (16 mmol) of freshly distilled phosphorus oxychloride, and 20 ml of ethylene dichloride was heated to 70° for 20 min with evolution of gas subsiding during that time. The mixture was diluted with chloroform and eluted rapidly through an alumina column (40 g of neutral, activity III) with chloroform. Heat was given off as the solution passed down the column. Two 70-ml fractions were collected, combined, and concentrated by evaporation of solvent. The liquid residue was short-path distilled [75° (0.1 mm)] producing 0.64 g (71%) of cyano ester **15**: ir (thin film) 2200 (C≡N), 1725 (C=O), and 1048 cm^{-1} (cyclopropyl CH_2); nmr (CCl_4, TMS internal) τ 6.27 (s, 3, OCH_3) and 7.4–8.9 [m (characteristic sharp peaks at 7.75, 8.08, 8.17, 8.66, and 8.75), 8]; mass spectrum (70 eV, heated inlet) M^+ at *m/e* 165.

Anal. Calcd for $C_9H_{11}O_2N$: C, 65.44; H, 6.71. Found: C, 65.54; H, 6.74.

5-Cyanobicyclo[3.1.0]hexane-1-carboxylic Acid (16).—Cyano-ester **15** was hydrolyzed in the usual manner as described in the preparation of **12**. The product was recrystallized from a mixture of ether-hexane giving 0.49 g (84%) of white crystalline **16**. The acid was further purified by recrystallization and sublimation [80° (0.01 mm)]: mp 117.0–118.5°; ir (Fluorolube mull) 2300–3300 (acid O—H), 2250 (C≡N), 1700 (C=O) and 1040 cm^{-1} (cyclopropyl CH_2); nmr (CCl_4, TMS internal) τ −2.2 (s, 1, acid proton) and 7.3–8.8 [m (characteristic sharp peaks at τ 7.93, 7.97, 8.61, and 8.70), 8].

Anal. Calcd for $C_8H_9O_2N$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.51; H, 5.99; N, 9.17.

Methyl Bicyclo[3.1.0]hexane-1-carboxylate (18).—To a solution of 4.03 g (24.5 mmol) of methyl 3-hydroxycyclohexane-1-carboxylate[7] in 40 ml of pyridine (freshly distilled from BaO) was added 5.2 g (26.5 mmol) of sublimed *p*-toluenesulfonyl chloride. The mixture was stirred for 15 hr at room temperature after which time a large amount of white pyridine hydrochloride had formed. Ice-cold 2 *N* sulfuric acid (50 ml) was added and the aqueous solution was then extracted with two 100-ml portions of ether. The combined ether extracts were washed with cold acid solution until the aqueous wash was acid to litmus paper. The ether extract was dried ($MgSO_4$) and concentrated to yield a slightly yellow, viscous liquid from which excess *p*-toluenesulfonyl chloride was removed by sublimation at 40° (0.1 mm). The product, **17**, remained as a viscous liquid (7.05 g, 90%): ir (thin film) 2900 (C—H), 1725 (C=O), 1190 and 1178 cm^{-1} (OTs); nmr (CCl_4, TMS internal) τ 2.26, 2.39, 2.70, and 2.84 (aromatic A_2B_2 pattern, 4), 5.1–5.9 (m, 1), 6.42 (s, 3, OCH_3), 7.56 (s, 3, CH_3), and 7.6–8.8 (m, 9).

To a solution of 7.05 g (22.8 mmol) of **17** in 30 ml of *t*-butyl alcohol was added dropwise 40 ml of a *t*-butyl alcohol solution of potassium *t*-butoxide [prepared from 1.0 g (25 mg-atoms) of potassium metal in 40 ml of *t*-butyl alcohol]. A white precipitate formed immediately upon addition. The mixture was stirred for 15 min after addition was complete. The mixture was filtered after addition of 50 ml of benzene. The filtrate was diluted with 150 ml of ether and washed with three 70-ml portions of distilled water. The organic layer was dried ($MgSO_4$) and concentrated to a low volume by flash evaporation. The residue was short-path distilled [60° (0.5 mm)] producing 2.275 g (71%) of colorless ester **18**: ir (thin film) 2900 (C—H), 1728 (C=O), 1145 (C—O), and 1040 cm^{-1} (cyclopropyl CH_2); nmr spectrum (CCl_4, TMS internal) τ 6.43 (s, 3, OCH_3), 7.7–8.5 (m, 6), 8.6–9.0 (m, 2), and 9.15–9.40 (m, 1); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 140.

Bicyclo[3.1.0]hexane-1-carboxylic Acid (19).—The saponification of **18** was carried out in a similar manner to that described for the preparation of **12**. From 1.0 g (7.14 mmol) of **18**, there was obtained 0.785 g (87%) of **19** as a colorless liquid after short-path distillation [100° (0.01 mm)]: ir (thin film) 2600–3300 (acid O—H), 1680 (C=O), and 1045 cm^{-1} (cyclopropyl CH_2); nmr (CCl_4, TMS internal) τ −2.8 (s, 1, acid proton), 7.7–8.8 [m, (characteristic sharp peak at τ 8.16), 8], and 9.05–9.30 (m, 1).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.59; H, 7.91.

Registry No.—**5**, 25090-39-5; **6**, 25090-40-8; **7**, 25090-41-9; **8**, 25090-42-0; **10**, 25090-43-1; **11**, 25090-44-2; **12**, 25090-45-3; **13**, 25090-46-4; **14**, 25090-47-5; **15**, 25090-48-6; **16**, 25090-49-7; **17**, 25090-50-0; **18**, 25090-51-1; **19**, 25090-52-2.

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A New Ring Enlargement Procedure. IV. The Decomposition of the Magnesium Salts of Various 1-(1-Bromoethyl)-1-cycloalkanols

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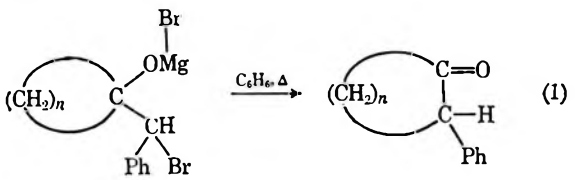
A new ring expansion procedure is described. Various ethylidenecycloalkanes were smoothly and easily converted to the halohydrins which in turn were simply transformed to the magnesium salts. The latter were decomposed to the ring enlarged 2-methyl ketones in good yields and high purity.

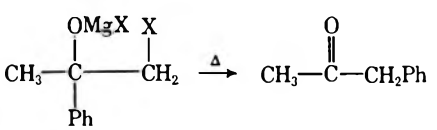
The utility of the carbocyclic ring expansion reactions in organic synthesis is undeniable. Fortunately, organic chemistry does furnish a variety of excellent methods[1] to effect ring enlargements. The method to be outlined herein, although entailing no new reaction nor reaction type for a ring expansion offers synthetic simplicity for its appeal and merit.

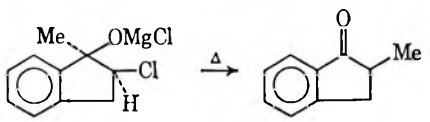
Two preliminary manuscripts[2,3] have demonstrated that the decomposition of the magnesium salts of the appropriate halohydrins unfolded a new procedure for ring expansion (eq 1). An additional preliminary result[4a] revealed that the magnesium salt of 1-bromomethyl-1-cyclohexanol did not yield the ring expanded ketone, cycloheptanone, but instead produced cyclohexanecarboxaldehyde. Lastly, the decomposition of the magnesium salt of 9-chloro-1-methyl-1-decalol (–O–H and –Cl *cis*) offers a new stereoselective method for the introduction of an angular methyl group.[4b] These results were in accord with the conclusions of Geissman and Akawie[5] who extensively studied the reaction producing ketones *via* the decomposition of the magnesium salts of halohydrins. They observed that primary halides do not rearrange unless a good migrating group is involved and that secondary and tertiary halides do rearrange regardless of the migrating group (eq 2). From their stereochemical studies they concluded that the halo and hydroxyl groups must be *cis* (or can attain the *cis* alignment in nonrigid systems) to effect the rearrangement. The *trans* isomer leads to extensive decomposition, thus, precluding an epoxide interpretation for the reaction and leaving, as plausible, a pinacol-type mechanism (eq 3).



$n = 4, 5, 6,$ and 7 (1)

(*via* epoxide) (2)



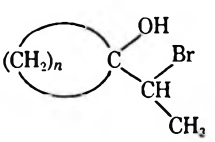


(3)

This manuscript extends the synthetic utility of the ring enlargement procedure and further tests the observations of Geissman and Akawie.[5]

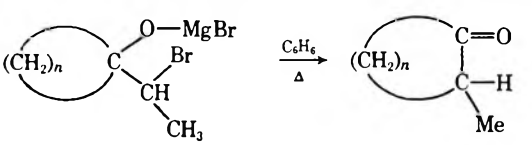
Results and Discussion

2-Methylcycloalkanones from Ethylidenecycloalkanes.—The halohydrins, **1**, necessary for the ring expansion were easily prepared by the treatment of the ethylidenecycloalkanes with N-bromosuccinimide and water at room temperature. The halohydrins, **1** (n = 4 and 5), were purified and characterized, the remaining one was used directly without purification. The halohydrins were converted to the magnesium salts (Grignard reagent) and subsequently decomposed producing the 2-methylcycloalkanones, **2**, in good yields (eq 4).



1

$n = 4, 5,$ and 6



2

$n = 4, 5,$ and 6 (4)

The results are presented in Table I. After distillation of the products, **2**, a polymeric residue remained, most probably due to the decomposition of unreacted halohydrin, **1**.

The structural assignments for the ketones, **2**, were based on the infrared spectra, the nmr spectra, and the 2,4-dinitrophenylhydrazones. The purity of each ketone was determined by vapor phase chromatography revealing that each ketone was no less than 92% pure. The major impurity in each instance was the isomeric carbonyl compound, **3** (vpc analysis). The ketone, **3**, was also detected, in each case, from the nmr spectra

(1) For an excellent recent review, see C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

(2) A. J. Sisti, *J. Org. Chem.*, **33**, 453 (1968).

(3) A. J. Sisti, *Tetrahedron Lett.*, **52**, 5327 (1967).

(4) (a) A. J. Sisti, *J. Org. Chem.*, **33**, 3953 (1968); (b) A. J. Sisti and A. Vitale, *Tetrahedron Lett.*, **54**, 2269 (1969).

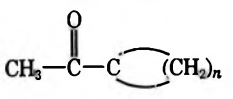
(5) T. A. Geissman and R. I. Akawie, *J. Amer. Chem. Soc.*, **73**, 1993 (1951).

TABLE I

RESULTS OF THE DECOMPOSITION OF THE MAGNESIUM SALTS OF 1

Compd 1	% yield of ketone 2	2,4-DNP mp, °C (lit.)	ν_{film}, cm^{-1}
4	65 (63)[a]	137–138[b]	1705
5	60 (60)[a]	120–121 (119–121)[c]	1700
6	(61)[a]	140–142 (140–141)[d]	1695

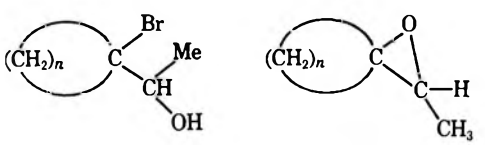
[a] Overall yield, based upon the ethylidenecycloalkane. [b] Compared with the 2,4-DNP of an authentic sample; no depression in melting point observed. [c] G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **83**, 599 (1961). [d] A. C. Cope and G. L. Woo, *ibid.*, **85**, 3601 (1963).



3

$n = 4, 5,$ and 6

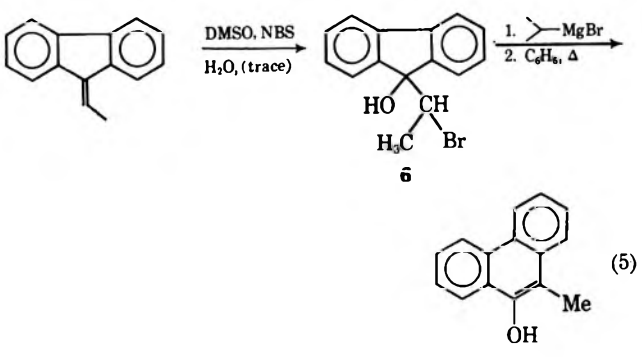
(sharp singlet at τ 7.9–8.0, methyl group adjacent to a carbonyl group). Authentic samples of **3** (n = 4 and 5) were shown to have the same retention time (vpc) as the minor contaminant from the reaction product. The origin of the production of **3** warrants a brief comment. Two reasonable paths are immediately apparent: first, the production of small amounts of the isomeric halohydrins, **4** (from the reaction of the ethylidenecycloalkanes with NBS and water), whose magnesium salts would yield **3** upon decomposition *via* a hydride shift; second, the formation of small amounts of the epoxides, **5**, from the decomposition of the magnesium salt of **1**, followed by a breakdown to **3**.



4 **5**

$n = 4, 5,$ and 6

10-Methyl-9-phenanthrol from 9-Ethylidenefluorene.—The halohydrin, **6**, necessary to accomplish the ring expansion was prepared by the new procedure of Dalton[6] (eq 5). It was subsequently converted to the magnesium salt and decomposed to yield 10-methyl-9-phenanthrol (**7**), in good yield (eq 5). The structure of the latter compound, **7**, was confirmed by its infrared spectrum, melting point, and conversion to a known derivative.



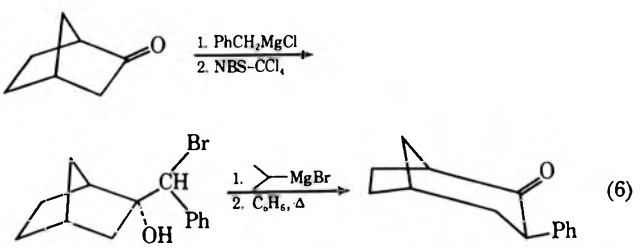
6

(5)

7

(6) D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Amer. Chem. Soc.*, **90**, 5498 (1968).

3-Methyl[3.2.1.]bicyclooctanone-2 from 2-Ethylidenenorbornane.—A broad spectrum of reaction types involving alkyl migrations toward incipient electron-deficient centers in the norbornyl system (ring expansion) have been studied. All reactions involving migrations to nitrogen[7] and carbon[8] conspicuously prefer methylene migration (less substituted, C-2–C-3 bond) over methine migration (more substituted, C-1–C-2 bond). Each of the above proceeds as indicated despite the generation of a relatively unfavorable boat transition state. Only the Baeyer–Villiger reaction with 2-norbornanone[9] is electronically controlled (C-1–C-2 bond migration). Sauers[9] has put forth an explanation for these apparent anomalies in the norbornyl system by proposing a third factor. The latter arises from the consideration of the torsional strain produced by nonbonded interactions between the eclipsed groups, on C-2 and the hydrogens on C-3. Thus, the migration of the C-2–C-3 bond produces a considerable easing of the nonbonded interactions. However, the migration of the C-1–C-2 bond would entail much less relief of strain because unfavorable interactions between C-2 and the bridgehead hydrogen are considerably less, since the dihedral angles involved are about 44 and 79°. The ring expansion procedure described herein was successfully tried on the norbornyl system and the results substantiated Sauers' new proposition. A previously communicated result,[3] namely, the decomposition of the magnesium salt of 2-(α-bromobenzyl)-2-norbornanol, (**8**), yielded *exclusively* 3-phenyl[3.2.1]-bicyclooctanone-2 (**9**) (eq 6) which results from the migration of the less substituted C-2–C-3 bond[10] and from the formation of a boat transition state. The present work on 2-ethylidenenorbornane entailed its conversion to the halohydrin,[11] **10** (NBS–H_2O method), which when converted to the magnesium salt and decomposed produced only 3-methyl[3.2.1]bicyclooctanone-2 (**11**) (eq 7). Similarly, this compound was produced from the migration of the less substituted, C-2–C-3 bond, which would also involve a boat transition state. The structure indicated for **11** was assigned on the basis of elemental analysis, the infrared spectrum,



8 **9**

(6)

(7) R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, **26**, 1703 (1961); C. L. Arcus, R. E. Marks, and R. Vitterlain, *Chem. Ind.* (London), 1193 (1960).

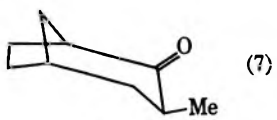
(8) R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963); J. Berson and D. Willner, *J. Amer. Chem. Soc.*, **84**, 675 (1962).

(9) R. R. Sauers and J. A. Beisler, *J. Org. Chem.*, **29**, 210 (1964).

(10) When the sequence outlined in eq 6 was pursued with 2-methylcyclopentanone, the expected preponderance of the product resulting from the migration of the *more substituted* bond to an electron-deficient center was encountered, namely, 2-phenyl-3-methylcyclohexane (unpublished results of Mr. George Rusch).

(11) The indicated stereochemical assignment for the halohydrin, **10**, was based on the following rationale: the approach of the reagent, NBS, to the 2-ethylidenenorbornane to produce the bromonium ion [see E. E. Van Temelen and K. B. Sharpless, *Tetrahedron Lett.*, 2655 (1967)], should be *exo;* thus, the water will attack from the *endo* position.

10



(7)

11

and nmr analysis. The migration of the more substituted carbon atom (C-1–C-2 migration in **10**) would result in the production of 2-methyl[3.2.1]bicyclooctanone-3 and not **11** as indicated (eq 7). The former was discarded on the basis of nmr studies. The nmr in carbon tetrachloride revealed a multiplet at τ 7.3–7.4 assigned to the bridgehead hydrogen α to a carbonyl group, and a multiplet at τ 7.5–7.6 assigned to the bridgehead hydrogen. The previous signal assignments were based upon the following observations. Bicyclo[3.2.1]octanone-2 in carbon tetrachloride exhibits signals at τ 7.3, multiplet corresponding to the bridgehead hydrogen α to a carbonyl group, and τ 7.5 multiplet corresponding to the bridgehead hydrogen, and the following signals reported[3] for **9**, τ 7.25 multiplet corresponding to the bridgehead hydrogen α to a carbonyl group, and τ 7.50 multiplet corresponding to the bridgehead hydrogen. Additional support for the structural assignment was obtained from deuterium exchange studies. The bicyclic ketone, **11**, was subjected to a treatment with trifluoroacetic acid-*d* (10% solution) for 24 hr at 100°. The nmr spectral analysis revealed that essentially one hydrogen was exchanged (the isomeric bicyclic ketone, 2-methyl[3.2.1]bicyclooctanone-3, should have exchanged three hydrogens).

Lastly, it is apparent that all the results herein substantiate the conclusion of Geissman and Akawie[5] that secondary halides rearrange regardless of the migrating group and indicate the simplicity of the conversion of exocyclic ethylidene compounds to the corresponding ring enlarged 2-methyl ketones.

Experimental Section[12]

1-(1-Bromoethyl)-1-cycloalkanols (**1**) were prepared from the appropriate ethylidenecycloalkanes (Columbia Organic Chemicals Co.) (0.15–0.25 mol), an equivalent amount of N-bromosuccinimide, and 100–150 ml of water according to a procedure previously described.[13] The halohydrins, **1**, were purified by distillation except for **1** (n = 6) which was used without purification.

The halohydrin, **1** (n = 4): bp 40–41° (0.4 mm) (70%); ir spectrum (film) 3450 cm^{-1} (-O—H); nmr (CCl_4) τ 5.7–6.1 (q, one hydrogen).

Anal. Calcd for $C_7H_{13}BrO$: C, 43.54; H, 6.78. Found: C, 43.30; H, 6.50.

For **1** (n = 5): bp 45–45° (0.1 mm) (67%); ir spectrum (film) 3500 cm^{-1} (-O—H); nmr (CCl_4) τ 5.7–6.1 (q, one hydrogen).

Anal. Calcd for $C_8H_{15}BrO$: C, 46.38; H, 7.25. Found: C, 46.15; H, 7.05.

For **1** (n = 6): ir spectrum (film) 3425 cm^{-1} (-O—H); nmr (CCl_4) τ 5.6–6.0 (q, one hydrogen).

2-(1-Bromoethyl)-2-norbornanol (**10**) was prepared by the procedure presented above except that 12.2 g (0.10 mol) of 2-ethylidenenorbornane (Chemical Samples Co.) was employed. The resultant halohydrin was used without purification: ir spectrum (film) 3450 cm^{-1} (-O—H); nmr (CCl_4) τ 5.5–6.0 (m, one hydrogen).

9-(1-Bromoethyl-9-fluorenol (**6**) was prepared with 19.2 g (0.10 mol) of 9-ethylidenefluorene (Aldrich Chemical Co.), 200 ml of DMSO, 2.8 ml of water, and 35 g (0.20 mol) of N-bromosuccinimide according to the method described by Dalton.[6] The halohydrin was not purified but was used directly: ir spectrum (film) 3450 cm^{-1} (-O—H); nmr (CCl_4) τ 5.6–6.0 (q, one hydrogen).

All the halohydrins gave immediate precipitates with alcoholic silver nitrate.

2-Methylcycloalkanones (**2**) were prepared by the dropwise addition of an equivalent amount of isopropylmagnesium bromide in ether to a cooled benzene (300 ml anhydrous) solution of the halohydrin, **1** (0.10 mol). After the dropwise addition of the Grignard reagent the solution was gently refluxed overnight and subsequently decomposed (NH_4Cl). The separated organic portion was washed successively with water, 10% sodium bicarbonate solution, and water, and then dried ($MgSO_4$). The solvent was removed under vacuum (rotary evaporator) and the residue distilled.

For **2** (n = 4): bp 50–52° (10–15 mm) (lit.[14] 163°) (65%); ir spectrum (film) 1705 cm^{-1} (C=O), ir spectrum (film) of an authentic sample of 2-methylcyclohexanone was identical with the preceding ir; nmr (CCl_4) sharp τ 8.9–9.0 [d, -C(=O)C(H)CH_3], τ 8.0 (small sharp s, H_3C—C=O); vpc (20% Carbowax, 150°, 40 spi) showed two peaks, 95% **2** (n = 4) and 5% **3** (n = 4), an authentic sample, methyl cyclopentyl ketone, had the same retention time as the minor component, **3** (n = 4).

For **2** (n = 5): bp 53–55° (7–8 mm) (lit.[15] 183°) (60%); ir spectrum (film) 1700 cm^{-1} (C=O); nmr (CCl_4) τ 9.0–9.1 (sharp d, -C(=O)C(H)CH_3), τ 8.0 (small sharp s, H_3C—C=O); vpc (20% Carbowax, 150°, 40 psi) showed two peaks 93% **2** (n = 5) and 7% **3** (n = 5), an authentic sample, methyl cyclohexyl ketone, had the same retention time as the impurity, **3** (n = 5).

For **2** (n = 6): bp 51–52° (0.9 mm) (lit.[16] 86–87° (12 mm) (61%); ir spectrum (film) 1695 cm^{-1} (C=O); nmr (CCl_4) τ 8.9–9.0 [sharp d, -C(=O)C(H)CH_3], τ 8.0 (small sharp s, H_3C—C=O); vpc (20% Carbowax, 200°, 40 psi) showed two peaks 92% **2** (n = 6) and 8% **3** (n = 6). The latter structural assignment (methylcycloheptyl ketone) was based on comparison with the preceding verified assignments.

9-Methyl-10-phenanthrol (**7**).—The halohydrin, **6**, was dissolved in anhydrous benzene (300 ml) and treated with an equivalent amount (0.10 mol) of isopropylmagnesium bromide in ether as described above except that the reflux time was curtailed to 5 hr. The residue was recrystallized from methanol–water, yielding 13 g (62%): mp 122–124° (lit.[17] mp 125°); ir spectrum ($CHCl_3$) 3580 cm^{-1} (-O—H). The acetate had mp 148–149° (lit.[17] 150–151°).

3-Methyl[3.2.1]bicyclooctanone-2 (**11**).—The halohydrin, **10**, was dissolved in 200 ml of anhydrous benzene to which was added an equivalent of isopropylmagnesium bromide in ether (0.10 mol) as previously described above except that the reflux period was for 2 hr. The residue was distilled, bp 59–61° (2.4 mm), yielding 9 g (65%) of a colorless oil: ir spectrum (film) 1710 cm^{-1} (C=O); nmr (CCl_4) τ 7.3–7.4 (m, bridgehead hydrogen α to a carbonyl group), τ 8.9–9.1 [d, -C(=O)C(H)CH_3]; vpc (20% Carbowax, 200°, 40 psi) showed the compound to be no less than 95% pure.

Anal. Calcd for $C_9H_{14}O$: C, 78.82; H, 10.21. Found: C, 78.89; H, 10.34.

The 2,4-dinitrophenylhydrazone had a melting point of 144–145.5° (ethanol).

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.55; H, 5.64; N, 17.58.

(12) All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Spectracord infrared spectrophotometer. The nmr spectra were determined with a Varian A-60 instrument.

(13) C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.*, **77**, 2549 (1955).

(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 362.

(15) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **83**, 599 (1961).

(16) A. C. Cope and G. L. Woo, *ibid.*, **85**, 3601 (1963).

(17) J. W. Cook, J. Jack, J. D. Loudon, G. L. Buchanan, and J. MacMillan, *J. Chem. Soc.*, 1397 (1951).

Before sealing a tube there was inserted 1 g of compound **11**, and 2 ml of trifluoroacetic acid-*d* (10% solution). The tube was placed in an oil bath for 24 hr at 100°, after which the contents were made basic by pouring into 10% sodium carbonate solution followed by extraction with ether. After drying ($MgSO_4$) and removing the ether, the nmr spectrum of the residue was taken. Upon comparison of the area, τ 7.3–8.2, with the undeuterated spectrum it was concluded that essentially one hydrogen was exchanged.

Registry No.—**1** (n = 4), 25090-34-0; **1** (n = 5), 25090-35-1; **1** (n = 6), 25090-36-2; **11**, 25111-12-0; **11** 2,4-DNP, 25111-13-1.

Exalted n–π* Transitions for Substituted Phenylacetones

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Received October 9, 1969

As the alkyl group in 1-phenylcyclopropyl alkyl ketones was changed in the series Me, Et, *i*-Pr, *t*-Bu, strong absorption due to conjugation of the phenyl group with the cyclopropane ring appeared. This conjugation produced absorption tailings which led to false exaltations in the n–π* region. A method is presented which aids in detection of such cases. The stronger acetyl–cyclopropane conjugation is suggested only for the methyl ketone and a value of 2 kcal appeared suitable. Although α′-alkylation of α-phenylacetones did not increase the ketonic absorption, α-alkylation appeared to do so and the possible reasons for this are discussed. The addition of methyllithium to diphenylacetic acids is not a satisfactory synthesis of diphenylacetones.

The fact that α-phenylacetone showed an increase of extinction coefficient (ε 150, EtOH) in the n–π* region (280–290 mμ) has received various interpretations. Cookson[1] originally proposed that such exaltations arose most significantly when the plane of the carbonyl group faced the plane of the benzene ring ($\theta = \psi = 90°$ as in Figure 1b). In contrast, it was proposed somewhat later[2] that there was involvement of the n electrons of oxygen. This leads, at least by the LCAO method, to a prediction that the oxygen should nearer the β,γ unsaturation for maximum exaltation. Still later,[3] a computer program, which calculated angular populations as a function of hydrogen–hydrogen repulsions and then evaluated several proposals for explaining exaltations, supported the Cookson view. The best equation (not stated explicitly in ref 3) was $\epsilon = 30 + 810 \sin^2\theta \sin^2\psi$, wherein ε is the observed extinction coefficient of an unstrained α-phenyl ketone in ethanol solution and the angles are those defined in Figure 1. Of the ketones examined, only 1-acetyl-1-phenylcyclopropane proved to be an exception. The present paper deals with the source of this difficulty and sets forth additional factors concerning application of the Cookson proposal.

Discussion of Results

The computer program gave no recognition to the fact that the acetyl group and the cyclopropane ring show conjugation in the bisected structure ($\psi = 0°$ or 180°). Such conjugation for cyclopropanecarboxaldehyde was estimated to be in excess of 2 kcal by Bartell.[4a] Such a conjugation term was inserted using the simple expression[4b] $E = -2.0 \cos^2\psi$ and found to yield acceptable results. Greater or lesser values of the maximum conjugation energy were less satisfactory: 0 kcal (ϵ_{calcd} 213.5), 1 (102.9), 1.5 (87.7), 2.0 (76.7), 2.5 (69.4). In an effort to obtain further support for this interpretation, there has been prepared a series of ketones with larger alkyl groups. These were expected to show increasing exaltations of the ketonic absorption due to adoption of conformation **1b** (90–90°). The numerical data of Table III (Experimental Section) seem to support such a result. Sought in the following paragraph, however, is a numerical method of deducing the correctness of such a conclusion. Such a method would be of use with literature reports which usually give only spectral values. When complete spectra are at hand, visual examination often suffices for estimation of the existence of a tailings contribution to the n–π* region. For this reason, complete spectra are given in Figure 2 for the four 1-acyl-1-phenylcyclopropanes. This figure suggests that true exaltations of the n–π* region are not obtained in the three new cases. Rather, extinction coefficients in both the benzenoid and carbonyl portions of the spectra are elevated by tailings of strong absorption in the 200-220-mμ region. Absorption in this region increased as R of RCO– was changed in the series Me, Et, *i*-Pr, *t*-Bu. This is due to increasing conjugation of the phenyl group with the cyclopropane ring. Thus, it is proposed that the conformation of the methyl ketone lies toward that with angles $\psi = 180°, \theta = 90°$ (Ac in the bisected structure), while that for the *t*-butyl ketone lies heaviest toward that with angles $\psi = 90° = 270°, \theta = 0°$ (Ph in the bisected structure). The small bathochromic shift of the ketonic band of the methyl ketone supports the former interpretation. The increased absorption shown by the four ketones in the 200-mμ region is interpreted as being due to increased phenyl–cyclopropane conjugation.[5] This proposal of an angular dependence seems at variance with the conclusion of Eastman[6] who observed little difference in the log ε plots for compounds of fixed geometry. It must be recalled, however, that the angular departures from the bisected structure

(1) R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956).

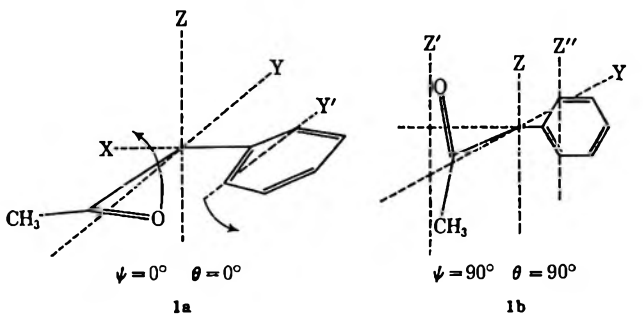
(2) H. Labhart and G. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).

(3) S. MacKenzie, S. F. Marsocci, and H. C. Lampe, *J. Org. Chem.*, **30**, 3328 (1965).

(4) (a) L. S. Bartell, B. L. Carroll, and J. P. Gillory, *Tetrahedron Lett.*, 705 (1964). (b) A similar equation was used to express the conjugation energy of twisted acetophenones: E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

(5) S. G. Beech, J. H. Turnbull, and W. Wilson, *ibid.*, 4686 (1952), reported for 1-methyl-2-phenylcyclopropane values of 230 mμ (ε >2500), 254 (1000), and 275 (320, EtOH). The energy of the phenyl–cyclopropane conjugation was given as 1.4 kcal by G. L. Closs and H. B. Klinger, *J. Amer. Chem. Soc.*, **87**, 3265 (1965).

(6) A. L. Goodman and R. H. Eastman, *ibid.*, **86**, 908 (1964).



1a 1b

Figure 1.—In structure **1a** all carbon atoms lie in the XY plane. Positive angles are defined as counterclockwise departures from this reference position, each axis of rotation being viewed from the group toward the origin of axes. Structure **1b** shows the proposed position which leads to the maximum exaltation of the n–π^* transition.

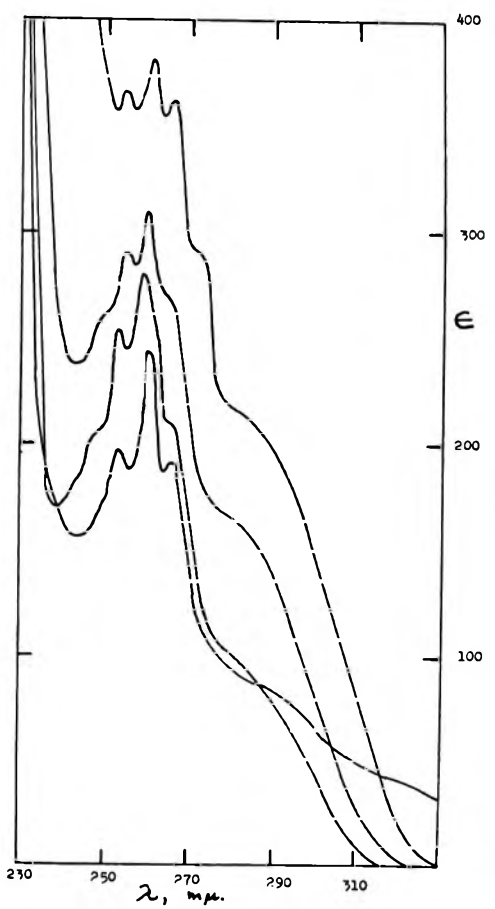
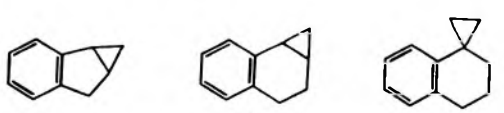


Figure 2.—Ultraviolet spectra for alkyl 1-phenylcyclopropyl ketones (curves are, in ascending order at 260 mμ, for R = Me, Et, *i*-Pr, *t*-Bu).

shown by **2**, **3**, and **4** are comparatively small in terms of $\cos^2\theta$. Moreover, inspection of the spectra of East-



	4	3	2
θ	25°	10°	0°
$\cos^2\theta$	0.82	0.97	1.00

man in the region of 230 mμ shows that the values of ϵ are highest for **2** and **3**, somewhat less for **4**, and definitely lower for phenylcyclopropane. It is therefore felt that the data of the present paper is not at variance with that of Eastman. The apparent difference lies mainly in the fact that the four ketones of the present work all have the same monosubstituted phenyl group and the small bathochromic shifts resulting from increased phenyl–cyclopropane conjugation are more easily seen.

Measurement of spectra in both cyclohexane and ethanol has been helpful in detection of other cases wherein spurious elevations of the n–π^* transition might arise. A term Δ is defined as $\epsilon_{EtOH} - \epsilon_{C_6H_{12}}$. For any ketone, two values are easily obtainable, Δ_{260} and Δ_{290}. The former, the solvent response of ϵ in the benzenoid region, is theoretically always zero and hence becomes useful for criticism of the latter.

$\Delta_{260} < \Delta_{290} > 0$.—The positive value of Δ_{290} is typical of n–π^* transitions exalted by reason of an accompanying charge-transfer transition around 200 mμ. The lower value of Δ_{260} gives assurance that the problem of tailings is minor. The majority of the ketones in Table I show such behavior.

$\Delta_{260} > \Delta_{290} > 0$.—If the charge-transfer absorption is at a longer than usual wavelength, tailings from such may cause spurious elevations. Such is the case for bis(1-phenylcyclopentyl) ketone and probably for benzobicyclo[2.2.2]octenones.

$\Delta_{260} \leqslant 0 \geqslant \Delta_{290}$.—The inference here is that any exaltation seen is not caused by the polar transitions described above. Data for the 1-phenylcyclopropyl alkyl ketones, where the alkyl group is Et, *i*-Pr, or *t*-Bu, fit in this group.

$\Delta_{260} > 0 > \Delta_{290}$.—This special case, seen in Table I only for 1-hydroxy-1,1-diphenyl-2-propanone, is assumed to arise when the polar solvent disrupts strongly a conformation preferred in cyclohexane because of hydrogen bonding. This might be seen for all α-hydroxy-α-phenylalkanones and study of this point is underway.

Data for ketones having spectral values in the first group were analyzed by the computer program which calculated, as a function of atomic repulsions, a 13 × 25 matrix of mole fractions, representing the populations at the possible angular positions. Also as before, each mole fraction was multiplied by $\sin^2\theta \sin^2\psi$ and the sum represented as $\Sigma \sin^2\theta \sin^2\psi$ in Table I. Values of this summation were not calculated for ethyl, isopropyl, or *t*-butyl ketones. The programs, requiring optimum fitting of the higher alkyl group at each angular position, are prohibitively complex. It is worthy of note, however, that such α' substitution on an α-phenyl ketone normally has little effect on ϵ for ketones with exalted n–π^* transitions. Three pairs of ketones in Table I illustrate this[7] and also suggest a lower per cent solvent sensitivity (% $\Delta_{290} = 100\Delta_{290}/\epsilon_{EtOH}$) for the higher ketone of each pair. Also of lower per cent solvent sensitivity are cycloalkanones and polyphenylacetones. This observation forced reexamination of data for triphenylacetone in cyclohexane, a solvent in which the ketone is only slightly soluble. Change of ϵ from 261[8] to 297 resulted. Values for $\epsilon_{C_6H_{12}}$, not ϵ_{EtOH} as in the previous study, are plotted in Figure 3

(7) Seen earlier for phenylacetone and ethyl benzyl ketone by D. Biquard, *Bull. Soc. Chim. Fr.*, **1941**, 55.

(8) S. MacKenzie, S. F. Marsocci, and P. R. Santurri, *J. Org. Chem.*, **28**, 717 (1963).

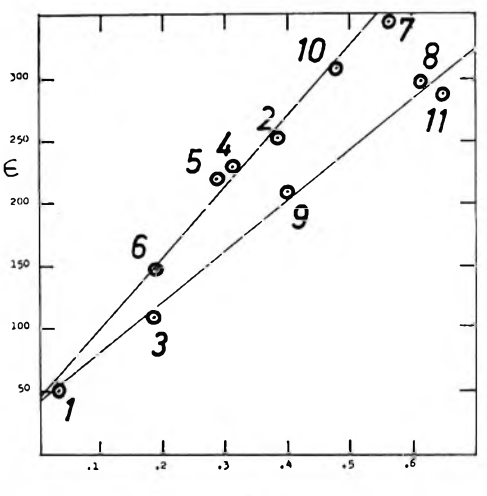
TABLE I

KETONES LISTED IN ORDER OF PER CENT CHANGE OF $\epsilon_{n-\pi^*}$ ON CHANGE OF SOLVENT

Compd no.	Ketone	Registry no.	Σ[a]	Δ_{280}[b]	Δ_{190}	% Δ_{280}[c]	Tailings
	Bis(1-phenylcyclopentyl) ketone			275	186	53	Strong
1	1-Acetyl-1-phenylcyclopropane[d]		0.033	40	25	33	Yes
2	1-Acetyl-1-phenylcyclobutane[d]	3972-67-6	0.384	56	103	29	No
3	Phenylacetone[e]		0.184	20	42	28	No
4	1-Acetyl-1-phenylcyclohexane[d]		0.310	42	84	27	No
5	1-Acetyl-1-phenylcyclopentane[d]		0.283	32	72	25	No
6	3-Methyl-3-phenyl-2-butanone		0.189	23	46	24	No
7	Dimethyl 1,2,3,4-tetrahydro-9-oxo-1,4-ethanoanthracene-7,8-exodicarboxylate[f]	25097-80-7	0.562		105	23	Presumed
	3-Phenyl-2-butanone			28	48	22	No
	1-Propionyl-1-phenylcyclohexane			15	63	19	No
	2,4-Dimethyl-2-phenyl-3-pentanone			20	34	17	No
	1-Propionyl-1-phenylcyclopentane			10	43	14	No
	2-Methyl-2-phenylcyclohexanone[g]				14	14	
	2,2,3-Trimethyl-5-phenylbicyclo[3.2.0]-hepten-3-one-6[h]			−47	100	13	
8	1,1,1-Triphenyl-2-propanone		0.61	23	40	12	Uncertain
	1,2,2,3-Tetramethyl-5-phenylbicyclo-[3.2.0]hepten-3-one-6[h]			44	45	10	
9	1,1-Diphenyl-2-propanone[e]		0.40	21	20	9	No
10	3,3-Diphenyl-2-butanone		0.48	40	17	5	No
11	2,2-Diphenylcyclopentanone		0.647	−17	13	4	No
	1-Pivalyl-1-phenylcyclopropane			−35	−28	−13	Yes
	1-Propionyl-1-phenylcyclopropane			−20	−20	−21	Yes
	1-Isobutyryl-1-phenylcyclopropane			−55	−61	−39	Yes
	1-Hydroxy-1,1-diphenyl-2-propanone			+142	−129	−38	Yes

[a] The first column is $\Sigma \sin^2\theta \sin^2\psi$ calculated by computer. For each angular setting, the value of $\sin^2\theta \sin^2\psi$ is multiplied by the mole fraction of ketone in that conformation, the mole fraction being based on calculated repulsion energies. [b] The term Δ is $\epsilon_{EtOH} - \epsilon_{C_6H_{12}}$ at the wavelength indicated. [c] The term % $\Delta_{290} = 100\Delta_{290}/\epsilon_{EtOH}$. [d] Reference 3. [e] Reference 8. [f] Reference 1. [g] Reference 13. [h] D. E. Bays and R. C. Cookson, *J. Chem. Soc. B*, 226 (1967).

against computer calculated values of $\Sigma \sin^2\theta \sin^2\psi$. Two lines are shown. The upper line has points for α-phenyl ketones which have at least one α-alkyl group. On the lower line are points for ketones without this feature. To explain this situation, two arguments can be advanced. Firstly, it can be assumed that the repulsion equations in the computer program do not correctly treat the forces between the rotors and an alkyl group on the same carbon. The computer program provides no flexibility or fitting of such groups. If this first explanation is correct, compounds with fixed ketone groups should have data falling on the lower line. This seems to be the case for 2,2-diphenylcyclopentanone.[9] For compounds with the benzobicyclo[2.2.2]octenone skeleton, data are inconclusive. Those for the compound of Cookson[1] (Table I) seem to lie closer to the upper line but for the parent compound was reported[10] 297 mμ (313, hexane) which would fall approximately between the two lines. However, the increased substitution of the phenyl ring and the tailings problem make these cases of questionable relevance. The value of $\Sigma \sin^2\theta \sin^2\psi$ for cyclohexanone with an axial phenyl (0.183 for ψ fixed at 120°) is too small to provide a clear decision between the two lines nor are spectral data altogether uniform.[11] A second explanation for the existence of two lines proposes that an α-alkyl group on an α-phenylketone increases the tendency of the phenyl group to interact with the ketone group.[12] This may result from a light decrease of the bond angle between Ph and Ac or from an inductive effect. This explanation suggests that the value of



$\Sigma \sin^2\theta \sin^2\psi$

Figure 3.—A plot of $\epsilon_{C_6H_{12}}$ against the value of $\Sigma \sin^2\theta \sin^2\psi$: (1) 1-acetyl-1-phenylcyclopropane, (2) 1-acetyl-1-phenylcyclobutane, (3) phenylacetone, (4) 1-acetyl-1-phenylcyclohexane, (5) 1-acetyl-1-phenylcyclopentane, (6) 2-methyl-2-phenyl-3-butanone, (7) a benzobicyclo[3.2.0]octenone (see Table I), (8) triphenylacetone, (9) diphenylacetone, (10) 2,2-diphenyl-3-butanone, (11) 2,2-diphenylcyclopentanone.

(9) Obtained through the courtesy of R. T. Conley, *Recl. Trav. Chim. Pays Bas*, **81**, 198 (1962).

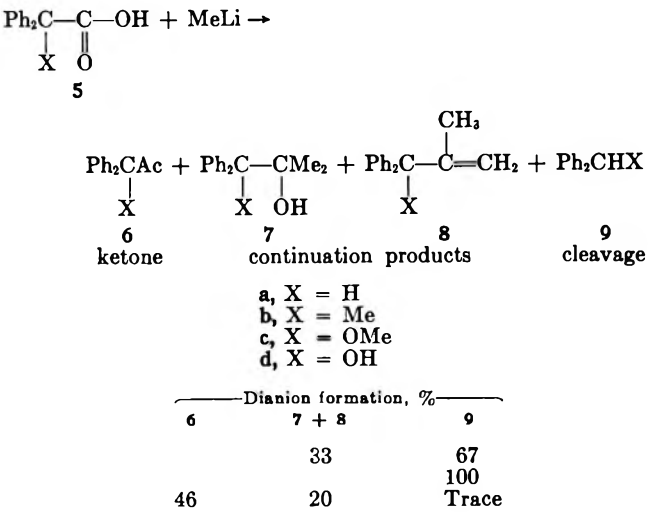
(10) K. Kitahonoki and Y. Takano, *Tetrahedron Lett.*, **24**, 1597 (1963).

(11) R. C. Cookson and J. Hudec, *J. Chem. Soc.*, **1962**, 429.

(12) When such a methyl group is directly on the donor, as in certain β,γ-unsaturated ketones, exaltations are increased.[1]

$\Sigma \sin^2\theta \sin^2\psi$ for 2,2-diphenylcyclopentanone is erroneous owing to the programming of the cyclopentane ring as planar. Puckering of the ring would lower the value toward that for the cyclohexane system. If, following this accomodation, the remaining values of $\Sigma \sin^2\theta \sin^2\psi$ are increased 15% for each alkyl group, a tolerably good agreement with linear behavior is obtained (plot not shown). Evidence favorable to this explanation exists. For example, 2-methyl-2-phenylcyclohexanone has a value of ϵ (100, EtOH)[13] almost as high as that for a cyclohexanone with a fixed axial phenyl,[14] this in spite of the fact that the main conformation should be equatorial phenyl and axial methyl. In a second example, a steroid which had an equatorial methyl in addition to an axial phenyl had the higher amplitude of its rotatory dispersion curve[11] although values of the extinction coefficients had the reversed order. This explanation led to reexamination of certain ketones useful in the present work. Values of ϵ (150, 160, EtOH) quoted[15] for 3-phenyl- and 3-methyl-3-phenyl-2-butanone have been revised upward (226, 193, EtOH) and that for 3,3-diphenyl-2-butanone (410, hexane)[15] revised downward (307, C_6H_{12}; 324, EtOH). The new data have been used in the tables and in Figure 3. Which of the two explanations represents the major factor is not, at present, known but this uncertainty should not lead, in our view, to the abandonment of the Cookson proposal. Other new evidence in favor of it can, after all, be cited. Observed[16] for 2-keto-2,3-paracyclophane were bands at 222 (15,300), 275 (380), and 307 (197) and for 2-keto-2,4-paracyclophane bands at 217 (13,100) and 285 (709). According to models, the latter compound can achieve a conformation near that shown by Figure 1b (90–90°) and the n–π^* band is strong. The former compound has a stronger charge-transfer band but a weaker n–π^* band. The angle ψ for the ketone group must be greater than 90° and is probably nearer to 120–150°. Consequently, the theory based on participation of the n electrons of oxygen, which calls for the greatest charge-transfer absorption at angular positions near 90–90° and the greatest n–π^* absorption at positions near 60–60°, may be wrong on both counts.

The search for a synthesis of certain substituted diphenylacetones led to study of the addition of organolithium compounds to acids, a useful synthesis of ketones pioneered by Gilman[17] and surveyed further by Tegner.[18] The method has been employed for synthesis of monophenylacetones.[3,18,19] It has now been found that the reaction is not generally applicable to diphenylacetic acids. The yields indicated above reflect the composition of the neutral fraction and hence are based on acid consumed. In the case of benzilic acid, the purity of the ketone could be increased by use of inverse addition but in the other cases this change did not alter the product composition.



Dianion formation, %		
6	7 + 8	9
	33	67
		100
46	20	Trace

Experimental Section

All ketones were examined by nmr spectroscopy using a Varian A-60 apparatus. Elementary analyses were performed by Micro-Analysis, Inc., Wilmington, Del. Ultraviolet spectra were taken of solutions in 95% ethanol and purified cyclohexane with a Beckman DK-2 apparatus which was also used in the previous papers in this series.

New ketones are described in Table II. Certain others were prepared following literature directions: 1-phenylcyclopropyl ethyl ketone,[20] 1-phenylcyclopentyl ethyl ketone,[20] 3-phenyl-2-butanone,[21] 3-methyl-3-phenyl-2-butanone[22] and 3,3-diphenyl-2-butanone.[23] The latter three ketones were regenerated from extensively recrystallized semicarbazones. From 1-cyano-1-phenylcyclopentane[24] was obtained bis(1-phenylcyclopentyl) ketone[25] in yields of 16% (*i*-PrMgBr) and 21.5% (*t*-BuMgCl). No volatile ketones could be isolated in these cases or with 1-cyano-1-phenylcyclohexane[26] and these reagents.

2,2-Diphenylpropanoic Acid, 5b.—To 0.85 mol of methyllithium was added with stirring 0.30 mol of diphenylacetic acid, **5a**. The solution became orange. The excess lithium wire was removed and there was added 0.70 mol of methyl iodide. The solution was refluxed 3 hr and allowed to stand overnight. It was poured into water and the ether layer separated and dried. Evaporation gave a white solid (0.35 g), tetraphenylethane. Acidification of the aqueous layer gave crude **5b** (49.2 g, 77%). It was recrystallized from 2:1 ethanol–water. The final yield of colorless acid, mp 177–178°,[27] was 34.5 g or 53%. When methyl iodide was not added, diphenylacetic acid could be recovered in 80% yield by pouring the ether into water and acidifying the aqueous layer.

1-Hydroxy-1,1-diphenyl-2-propanone, 6d.—To 1500 ml of ether containing 0.975 mol of methyllithium was added a solution of 41.4 g (0.18 mol) of benzilic acid, **5d**, in 500 ml of ether. The color, momentarily gray, changed quickly to purple. The solution was allowed to stand overnight. It was poured onto ice. Acidification of the water layer gave no **5d**. Evaporation of the ether layer gave 41.1 g of liquid residue which was distilled under reduced pressure (0.1 mm). Although little change of boiling point was seen, three fractions were collected: bp 130° (18.3 g), 130° (7.9 g), and slightly above 130° (3.0 g). The third fraction

(13) P. Colard, I. Elphimoff-Felkin, and M. Verrier, *Bull. Soc. Chim. Fr.*, 516 (1961).

(14) For 2,2-diphenylcyclohexanone 125 was reported (EtOH): W. B. Bennet and A. Burger, *J. Amer. Chem. Soc.*, **76**, 84 (1954).

(15) Extracted from small-scale graphs by the authors of ref 1.

(16) D. J. Cram and R. C. Hegeson, *J. Amer. Chem. Soc.*, **88**, 3515 (1966).

(17) H. Gilman and P. R. Van Ess, *ibid.*, **55**, 1258 (1933).

(18) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

(19) K. Mislow and C. L. Hamermesh, *J. Amer. Chem. Soc.*, **77**, 1590 (1955).

(20) P. Läuger, M. Frost, and R. Charlier, *Helv. Chim. Acta.*, **42**, 2394 (1959).

(21) C. M. Suter and A. W. Weston, *J. Amer. Chem. Soc.*, **64**, 535 (1942).

(22) W. D. Kumler, L. A. Strait, and E. L. Alpen, *ibid.*, **72**, 1463, 4558 (1950).

(23) K. Sisido and H. Nozaki, *ibid.*, **70**, 776 (1948).

(24) C. H. Tilford, M. G. Van Campen, and R. S. Shelton, *ibid.*, **69**, 2902 (1947).

(25) While this work was in progress, a detailed study of this ketone was reported: J. W. Wilt, H. Philip, and D. G. Shultenover, *J. Org. Chem.*, **33**, 1666 (1968).

(26) A. W. Weston, *J. Amer. Chem. Soc.*, **68**, 2345 (1946).

(27) D. E. Batemen and C. S. Marvel, *ibid.*, **49**, 2914 (1927), reported 173–174°.

TABLE II
KETONES FROM NITRILES AND RMgX

$(CH_2)_{n-1}CPhCOR$	Registry no.	Yield, %	Bp or mp (mm), °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
n = 3, R = Et		56	[a]						
Semicarbazone	25097-58-9		164–165	67.50	7.40	18.16	67.43	7.44	17.97
n = 3, R = i-Pr		40	62–64 (0.1)	82.93	8.56		83.10	8.35	
Semicarbazone	25097-59-0		194–195	68.54	7.70	17.13	68.60	7.67	16.99
n = 3, R = t-Bu		20	70–72 (0.1)	83.12	8.97		82.79	8.96	
n = 6, R = Et		69	91–92 (0.1)	83.29	9.32		83.20	9.19	
$Me_2CPhCOi$-Pr[b]	25097-60-3	32	80–82 (0.1)	82.05	9.53		82.18	9.38	

[a] Reference 20. [b] Did not form a semicarbazone.

TABLE III
SPECTRAL VALUES FOR PHENYLATED ACETONES AND CYCLOALKANONES[a]

Ketone $(CH_2)_{n-1}CPhCOR$	Registry no.	C_6H_{12}	95% EtOH
n = 3, R = Me[b]	1007-71-2	260 (205) 288 (50)	260 (245) 289 (75)
R = Et	25097-62-5	259 (296) 285 (114)	259 (276) 285 (94)
R = i-Pr	25097-63-6	261 (366) 285 (216)	260 (311) 285 (155)
R = t-Bu	25097-64-7	267 (396) 285 (238)	266 (361) 285 (210)
n = 5, R = Me[b]	4046-09-7	260 (220) 296 (220)	260 (252) 291 (292)
R = Et	17206-41-6	261 (239) 295 (268)	260 (249) 292 (311)
n = 6, R = Me[b]	3183-57-1	260 (208) 298 (230)	260 (250) 290 (314)
R = Et	2886-61-5	258 (225) 294 (274)	259 (240) 293 (337)
Bis(1-phenylcyclopentyl)	15811-02-6	261 (515) 295 (164)	261 (790) 290 (350)
		223 (18000)	225 (13800)
$AcCH_2Ph$[c]	103-79-7	260 (235) 289 (108)	258 (255) 283 (150)
AcCH(Ph)Me	769-59-5	258 (210) 289 (177)	258 (238) 283 (226)
$AcC(Ph)Me_2$	770-85-4	261 (211) 292 (147)	258 (234) 285 (193)
i-$PrCOC(Ph)Me_2$	25097-60-3	260 (215) 295 (164)	258 (235) 292 (198)
Ph_2CHAc[c]	781-35-1	260 (485) 292 (210)	260 (506) 287 (230)
Ph_2CMeAc	2575-20-4	260 (460) 298 (307)	260 (500) 292 (324)
$Ph_2C(OH)Ac$	4571-02-2	259 (355) 284 (468)	258 (497) 290 (339)[d]
Ph_3CAc	795-36-8	261 (912) 300 (297)	260 (935) 295 (337)
2,2-Diphenylcyclopentanone	15324-42-2	260 (582) 305 (288)	259 (565) 305 (301)

[a] Values are wavelength in mμ and, in parentheses, molar extinction coefficient at maxima. Certain literature values are used without alteration and reference is accordingly made. [b] Reference 3. [c] Reference 8. [d] Quite close to the value for an ethanol solution given in ref 13.

solidified after a few days. The solid was recrystallized three times from cyclohexane to give colorless crystals, mp 91–92°, 0.5 g, with an nmr spectrum with four bands: 7.2 (10 complex), 2.70 (1 s), 2.08 (1 s), and 1.20 (6 s). The melting point reported for 1,1-diphenyl-2-methylpropanediol-1,2 is 91–92°.[28] Nmr analysis of fraction 1 using the upfield bands for methyl hydrogens indicated that the ratio of ketone to glycol was about 3:1. The ratio for fraction 2 was 2:1. These two fractions were combined and refluxed 14 hr with hydroxylamine hydrochloride (8.0 g) and sodium acetate trihydrate (15.7 g) in 200 ml of 50% ethanol. About 50% of the solvent was removed by distillation. The crude residue (23 g), obtained slowly by cooling, was recrystallized from 500 ml of ligroin. The crystals weighed 9.6 g. These were recrystallized from 250 ml of 60% ethanol. The yield of pure oxime, mp 165° (lit.[29] 159–160°), was 8.2 g. In contrast to the oxime prepared by inverse addition described below, it did not yellow slightly in air. The oxime was mixed with 250 ml of water and 3.5 g of pyruvic acid and refluxed 5 hr. The cooled solution was extracted with ether which was washed with sodium bicarbonate solution, dried, and evaporated. Vacuum distillation gave 3.9 g of ketone which soon solidified. Crystallization from ligroin gave massive crystals, mp 64–65° (lit.[30] 63.5°). The nmr spectrum had three bands: 7.02 (10 s), 4.60 (1 s), and 1.83 (3 s). Inverse addition of 0.206 mol of methyllithium to 0.069 mol of **5d** gave 7.1 g of recovered **5d** and 6.1 g of a pale yellow oil, bp 130° (0.1 mm). Spectral examination suggested that this oil contained no glycol but did contain some benzophenone. The oil gave the oxime as before, but this yellowed in air.

Addition of Methyllithium Solution to Diphenylmethoxyacetic Acid, 5c.—No difference was seen between forward and inverse addition. Methyllithium (0.122 mol) was added to 0.06 mol of **5c**. There was obtained 8.0 g of recovered **5c** and 2.9 g of a pale yellow oil which contained about 40% 1,1-diphenylethanol, 35% methyl benzhydryl ether, and up to 35% benzophenone. The first two compounds were isolated by chromatography followed by crystallization.

Addition of 2,2-Diphenylpropanoic Acid to Methyllithium.—A solution of 0.136 mol of MeLi was added to 0.068 mol of **5b**. There was obtained 10.2 g of recovered **5b** and 2.8 g of a yellow oil. Analysis of the nmr spectrum suggested that this oil was comprised of 37% 1,1-diphenylethane, 22% 3,3-diphenyl-2-methyl-2-butanol, and 11% 3,3-diphenyl-2-methyl-1-butene. A portion of the 1,1-diphenylethane was isolated by chromatography. Neither continuation product was isolated.

Registry No.—1,2,2,3-Tetramethyl-5-phenylbicyclo[3.2.0]hepten-3-one-6, 25097-81-8; 2-methyl-2-phenylcyclohexanone, 17206-54-1; 2,2,3-trimethyl-5-phenylbicyclo[3.2.0]hepten-3-one-6, 25097-78-3.

(28) H. Meerwein, *Justus Liebigs Ann. Chem.*, **396**, 200 (1913).
(29) T. I. Temnikova, *J. Gen. Chem. USSR*, **15**, 514 (1945).
(30) C. L. Stevens and C. T. Lenk, *J. Org. Chem.*, **19**, 538 (1954).

Chemistry of Ylides. XX. Triphenylarsonium Phenacylide

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Triphenylarsonium phenacylide (I) has been prepared by two routes, and its chemical properties have been studied. It undergoes hydrolysis, thermal decomposition, O-alkylation, and C- or O-acylation. Reaction with carbonyl compounds normally affords olefins by ylide attack on the carbonyl carbon but with α,β-unsaturated carbonyl compounds a Michael addition occurs affording cyclopropanes.

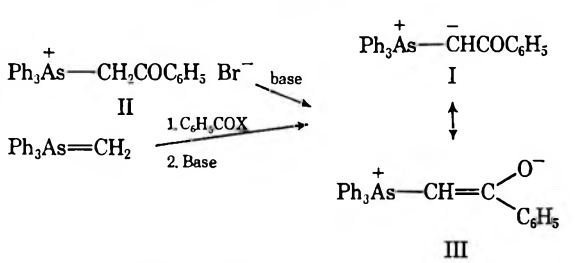
Although the first arsonium ylide appears to have been prepared in 1902[1] but not assigned its correct structure until 1950,[2] no more than 11 references were cited in the most recent (1966) review of arsenic ylide chemistry.[3] By now approximately 16 different arsonium ylides have been prepared but only about half have been isolated. As was pointed out in 1966,[3] and as remains true today, very little is known of the general chemistry and physical properties of arsonium ylides. This is in contrast with the large amount of information available for ylides of sulfur and phosphorus.

Interest in the chemistry of the ylides of arsenic continues because, based on the meager information presently available, arsenic seems to lie between sulfur and phosphorus in its effect on the properties of ylides. A study of arsenic ylide chemistry may discover unique chemical or physical properties and/or shed light on the mechanism of reactions of phosphorus or sulfur ylides, both of which results would have recognized importance in preparative organic chemistry.

This report relates some of the general chemistry of triphenylarsonium phenacylide (I), a stable, isolable arsenic ylide. It lays the base for further detailed studies of such ylides and their reactions.

Results and Discussion

Quaternization of triphenylarsine with phenacyl bromide afforded the known[3,4] arsonium salt II. Treatment of this salt with sodium ethoxide in benzene effected the proton abstraction and afforded the crystalline ylide I of mp 172–173°. Prior reports quoted melting points ranging from 154 to 183°.[2,5,6] The ylide I also could be prepared by acylating triphenylarsonium methylide with benzoyl chloride, benzoic anhydride, or ethyl benzoate.



The carbonyl absorption for the ylide salt II was at 1660 cm^{-1} whereas that for the ylide was at 1570 cm^{-1}, indicating a significant contribution of the enolate structure III and accounting for some of the stability of the ylide. The nuclear magnetic resonance (nmr) spectrum showed 20 aryl protons at δ 7.2–8.1 and the single methine proton at δ 4.75. The methine absorption was quite broad unless the sample and the solvent were especially dry, probably owing to proton exchange. Recently we reported such exchange for the analogous phosphonium ylide.[7]

The ylide I was stable to the atmosphere. However, warming the ylide in aqueous ethanol led to hydrolysis to triphenylarsine oxide and acetophenone, a cleavage typical of phosphonium ylides.[3] Treatment of a solution of the ylide with oxygen over extended periods of time resulted in no reaction but treatment with ozone resulted in oxidative cleavage to triphenylarsine oxide and phenyl glyoxal. Accordingly, the ylide seemed to show a sensitivity to hydrolysis and oxidation virtually identical with that shown by triphenylphosphonium phenacylide.[8]

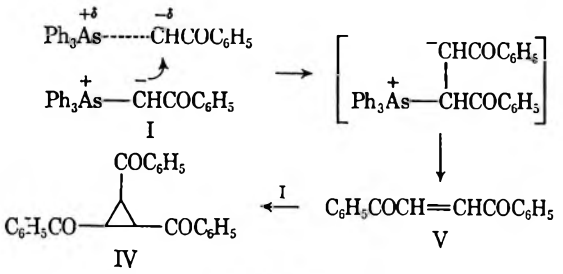
The thermal stability of the ylide I was investigated. Heating the pure ylide to 200° led to decomposition with triphenylarsine being the only identifiable product. The ylide could be recovered unchanged after extended heating in benzene solution but on heating in toluene solution, with or without the presence of copper sulfate, a high yield of *trans*-1,2,3-tribenzoylcyclopropane (IV) and triphenylarsine could be obtained. In this behavior the arsonium ylide I was identical with the analogous sulfonium phenacylide[9] but different from the phosphonium phenacylide which was stable to these conditions.

To account for the decomposition we propose the ylide commenced to dissociate *via* a carbenoid intermediate which quickly was attacked by another nucleophilic ylide molecule (Scheme I). The resulting betaine would eliminate triphenylarsine to afford 1,2-dibenzoylethene (V). Michael addition of additional ylide I to the olefin V would afford the observed product IV. In a separate experiment the latter reaction was found to proceed rapidly and quantitatively. However, an attempt to trap the olefin V with 2,5-diphenylisobenzofuran in a decomposition reaction failed.

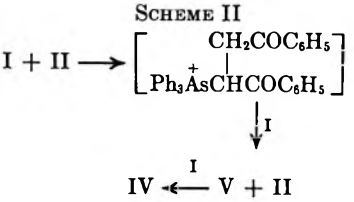
An alternative mechanism which must be considered is shown in Scheme II. This proposal involves essentially a chain reaction with a minute amount of ylide salt II formed from any source, perhaps even by reaction of traces of water with ylide, serving as the chain-carrying agent. This mechanism was shown to

(1) A. Michaelis, *Justus Liebigs Ann. Chem.*, **321**, 174 (1902).
(2) F. Krohnke, *Chem. Ber.*, **83**, 291 (1950).
(3) A. Wm. Johnson, "Ylid Chemistry," Academic Press, New York and London, 1966, pp 288–299.
(4) G. Aksnes and J. Songstad, *Acta Chem. Scand.*, **18**, 655 (1964).
(5) N. A. Nesmeyanov, V. V. Pravdina, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **155**, 1364 (1964).
(6) N. A. Nesmeyanov, V. V. Pravdina, and O. A. Reutov, *Izv. Akad. Nauk SSSR*, 1474 (1965).
(7) F. J. Randall and A. Wm. Johnson, *Tetrahedron Lett.*, 2841 (1968).
(8) F. Ramirez, R. B. Mitra, and N. B. Desai, *J. Amer. Chem. Soc.*, **82**, 5763 (1960).
(9) Paper XIX in this series: A. W. Johnson and R. T. Amel, *J. Org Chem.*, **34**, 1240 (1969).

SCHEME I

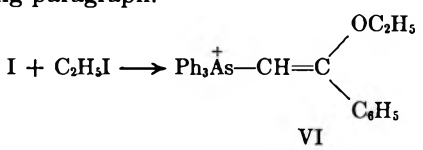


SCHEME II

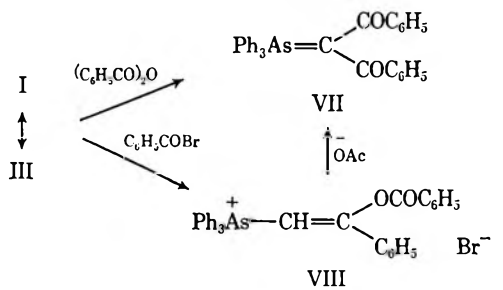


be possible by the observation that reaction of the ylide I with phenacyl bromide or with the conjugate acid of the ylide did afford the cyclopropane IV. There appears to be no simple means, perhaps other than a kinetic study, of distinguishing between the two possible mechanisms.[10]

The nucleophilic character of the ylide I was demonstrated by its undergoing an alkylation. Reaction with ethyl iodide afforded the O-ethyl product VI, the structure of which was proven by ir and nmr spectra and by hydrolysis to triphenylphenacylarsonium iodide. This result is identical with the O-alkylation found for the phosphonium phenacylide[11] but contrasts with the C-alkylation we reported for the sulfonium phenacylide.[9] Furthermore, it contrasts with the apparent C-alkylation of I by phenacyl bormide as postulated in the preceding paragraph.



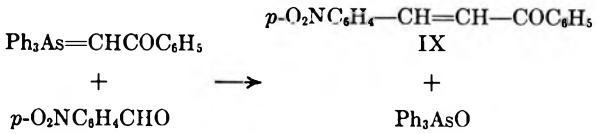
The ylide I also underwent acylation, the course of which depended on the reagent used. Reaction with benzoic anhydride afforded dibenzoylmethylenetriphenylarsenane (VII), presumably *via* initial C-benzoylation followed by proton abstraction from the new arsonium salt. The dibenzoylmethyltriphenylarsonium salt would be the most acidic species present and could suffer loss of a proton to the benzoate ion or to ylide I, thereby affording the new, highly stabilized ylide VII. Similar behavior was observed using acetic anhydride, benzoylacetylmethylenetriphenylarsenane being the product.



(10) C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **83**, 4033 (1961).
(11) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

Benzoylation of the ylide I with benzoyl bromide effected an O-acylation affording the enol benzoate VIII. The structure of VIII was proven by its ir spectrum (ν_{CO} 1745 cm^{-1}), the nmr spectrum showing a methine proton (δ 6.45 ppm), and by isomerization of VIII to the C-benzoylated product VII in the presence of sodium acetate. This rearrangement probably involves conversion of a kinetically controlled product VIII to the thermodynamically controlled product VII as was reported for the triphenylphosphonium phenacylide system.[12]

One of our major interests in exploring arsonium ylide chemistry is to ascertain how such ylides react with carbonyl compounds. Phosphonium ylides have long been known to afford olefins in such reactions (Wittig Reaction), presumably *via* a betaine adduct X intermediate.[13] Sulfonium ylides have been shown to afford epoxides under similar conditions, presumably *via* a similar intermediate.[14] Based on the few reports[15] to date on their reaction in which either olefin, epoxide, or both are formed upon reaction with carbonyl compounds, arsonium ylides seem intermediate in character between phosphonium and sulfonium ylides. Preparatory to exploring this unique position in depth, we have observed that triphenylarsonium phenacylide (I) reacts with *p*-nitrobenzaldehyde to form exclusively the olefinic product, *trans*-*p*-nitrobenzalacetophenenone (IX), and triphenylarsine oxide in high yield with no evidence of the formation of an epoxide or an arsine.

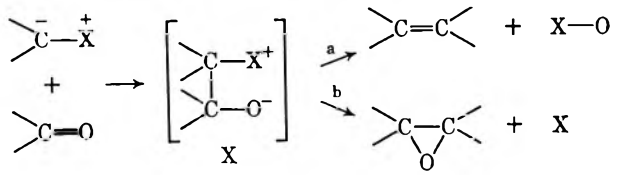


The results to date indicate that stabilized arsonium ylides, such as the phenacylide, carbomethoxymethylide,[15b] fluorenylide,[15c] and cyclopentadienylide,[15e] afford only olefinic products upon reaction with carbonyl compounds. The nonstabilized arsonium ylides, such as the methylide[15a] and ethylide,[15f] afforded almost exclusively epoxides (or products resulting from their rearrangement). However, a semistabilized arsonium ylide, the benzylide,[15d] has afforded approximately equimolar amounts of epoxide and olefin. Clearly, the nature of the carbanion fragment of the arsonium ylide is having a major influence on the course of the reaction. It is reasonable to suppose a two-step mechanism (Scheme III) is involved in the reactions of phosphonium, sulfonium, and arsonium ylides with carbonyl compounds. Therefore, since the product-determining step must be the second step in such a mechanism, the nature of the carbanion substituent must be affecting that step in an important manner.

No evidence is available to indicate how the carbanion substituent in arsonium ylides affects the distribution between path a and path b in Scheme III. It is conceivable that the "normal" path is b since triphenylarsine is not an especially strong oxygen scavenger as is

(12) P. A. Chopard, R. J. G. Searle, and F. H. Devitt, *ibid.*, **30**, 1015 (1965).
(13) Reference 3, pp 132–192.
(14) Reference 3, pp 304–366.
(15) (a) M. C. Henry and G. Wittig, *J. Amer. Chem. Soc.*, **82**, 563 (1960); (b) Y. T. Huang, W. Y. Ting, and H. S. Cheng, *Acta Chim. Sinica*, **31**, 37 (1965); (c) A. Wm. Johnson, *J. Org. Chem.*, **25**, 183 (1960); (d) A. W. Johnson and J. O. Martin, *Chem. Ind.* (London), 1726 (1965); (e) D. Lloyd and M. I. C. Singer, *ibid.*, 510 (1967). (f) A. Maccioni and M. Secci, *Chem. Abstr.*, **63**, 5674 (1965).

SCHEME III



triphenylphosphine. However, with the presence of a conjugating group on one of the carbon atoms of the betaine X, sufficient stabilization may be provided for the incipient double bond in the transition state for path a to increase the ratio of path a product to path b product. We are exploring the nature of this reaction further.

Experimental Section

Triphenylarsonium Phenacylide (I).—A homogeneous solution of 6.1 g (20 mmol) of triphenylarsine and 4.4 g (22 mmol) of phenacyl bromide in 30 ml of benzene was heated under reflux for 4 hr. The resulting precipitate of 6.2 g (56%) of phenacyltriphenylarsonium bromide (II) was removed by filtration and a sample was recrystallized from chloroform–benzene to mp 185° (lit.[4] mp 186°): ν_{CO} 1660 cm^{-1}; nmr absorption at δ 6.45 (area 2.0, methylene singlet) and 7.3–8.3 (area 20.7, aromatic multiplet).

To a solution of 0.9 g (2 mmol) of methyltriphenylarsonium iodide (prepared from methyl iodide and triphenylarsine) in 40 ml of benzene was added 10 mmol of potassium *t*-butoxide. After stirring for 10 min 0.3 g (2 mmol) of ethyl benzoate was added to the yellow solution. After stirring for 1 hr the excess butoxide was decomposed with ethanol, and the reaction was flooded with water and then acidified with hydrobromic acid. Extraction with chloroform and then evaporation of this solvent afforded 0.5 g (50%) of crude arsonium salt II which showed mp 180–182° after one crystallization.

To a slurry of 11 g (22 mmol) of II in 100 ml of dry benzene containing 0.5 ml of absolute ethanol was added 5 g of sodium hydride in mineral oil (50% slurry). After stirring overnight most of the solid material had dissolved and the solution had become a deep yellow color. The remaining precipitate was removed by filtration after which the filtrate was diluted with hexane to precipitate 9 g (95%) of the ylide I. The ylide was recrystallized from benzene–hexane as pale yellow microcrystals: mp 172–173° (lit.[2] mp 182–183°; lit.[5] mp 154–156°; lit.[6] mp 167–169°); ν_{CO} 1570 cm^{-1}; nmr absorption in alumina-dried $CDCl_3$ at δ 4.75 (area 1, methine singlet of half-width 1 cps) and 7.2–8.1 (area 20.2, aromatic multiplet). The methine singlet for a twice-recrystallized sample had a half-width of 4 cps unless the $CDCl_3$ first was shaken with alumina.

Warming a solution of 0.85 g of ylide I in 10 ml of aqueous ethanol and then extraction with chloroform left no organic matter in the aqueous phase. Evaporation of the chloroform and extraction of the oily residue with pentane afforded a solution of acetophenone as identified by infrared comparison with an authentic sample. The pentane-insoluble material was identified as triphenylarsine oxide by infrared spectral comparison with an authentic sample.

Ozonolysis of 0.85 g (2 mmol) of ylide I in 40 ml of methylene chloride at −70° led to the loss of the yellow color. The solvent was evaporated and a 2,4-dinitrophenylhydrazone was prepared in ethanolic solution. The red derivative crystallized from dimethylformamide–nitromethane, mp 292–294°, and appeared to be the bis-2,4-dinitrophenylhydrazone of phenyl glyoxal.

Anal. Calcd for $C_{20}H_{14}O_8N_8$: C, 48.59; H, 2.85; N, 22.66. Found: C, 48.66; H, 2.94; N, 22.30.

After the preparation of the derivative, triphenylarsine oxide was isolated from the filtrate by chromatography on alumina and was identified by melting point (197–198°) and comparison of its infrared spectrum with that of an authentic sample.

Thermolysis of Ylide I.—A solution of 4.2 g (1 mmol) of ylide I in 20 ml of toluene was heated under reflux for 2 days. During this time samples were withdrawn, and it was noted that the ylide carbonyl absorption at 1570 cm^{-1} gradually disappeared as a new carbonyl absorption at 1670 cm^{-1} gradually appeared and increased in intensity. Evaporation of the solvent and chromatography of the residue on alumina afforded 0.11 g (100%) of crude *trans*-1,2,3-tribenzoylcyclopropane (IV) which crystallized from benzene–heptane as colorless needles, mp 215° (lit.[16] mp 215°), ν_{CO} 1665 cm^{-1}, and was proven identical with an authentic sample by admixture melting point and comparison of infrared spectra.

A solution of 0.42 g (1 mmol) of ylide I and 0.24 g (1 mmol) of dibenzoylethylene in 20 ml of benzene was stirred for 24 hr at room temperature. Evaporation of the solvent and chromatography of the residue on alumina afforded a quantitative yield of IV.

To a stirred solution of 0.6 g (3 mmol) of phenacyl bromide in 30 ml of benzene was added 0.85 g (2 mmol) of ylide I. A precipitate began to form immediately and after 10 hr a total of 0.6 g of ylide salt II was obtained. Chromatography of the filtrate afforded 0.12 g of IV. Repetition of the reaction, but using the ylide salt II in place of the phenacyl bromide, again afforded the cyclopropane derivative IV.

Alkylation of Ylide I with Ethyl Iodide.—A solution of 1.3 g (3 mmol) of ylide I and 3 ml of ethyl iodide in 20 ml of methylene chloride was heated under reflux for 10 hr. Addition of ether afforded 1.3 g (75%) of crude β-(α-ethoxy)styryltriphenylarsonium iodide (VI) which was recrystallized from chloroform–ether as a colorless powder, mp 159–160°, $\nu_{C=C}$ 1590 cm^{-1}, with nmr absorption in $CDCl_3$ at δ 7.5–7.8 (area 20, aromatic multiplet), 5.78 (area 1, methine singlet), 3.66 (area 2, methylene quartet, J = 7 cps), 0.66 (area 3.1, methyl triplet, J = 7 cps). Use of a higher boiling solvent, such as benzene or toluene, in the alkylation also afforded some of the desired alkylation product VI but it was contaminated with considerable thermal decomposition product IV.

Anal. Calcd for $C_{28}H_{26}AsIO$: C, 57.95; H, 4.52; I, 21.87. Found: C, 57.86; H, 4.65; I, 21.94.

Hydrolysis of 0.4 g (0.7 mmol) of the alkylation product VI by warming in 20 ml of ethanol containing 5 ml of 47% hydriodic acid afforded 0.3 g (80%) of phenacyltriphenylarsonium iodide, mp 140°.

Acylation of Ylide I. A. With Benzoyl Bromide.—Addition of 0.2 g (1.1 mmol) of benzoyl bromide to 0.4 g (1 mmol) of ylide I in 10 ml of benzene resulted in the formation of an immediate precipitate (0.4 g, 70%) of the enol benzoate VIII. Crystallization from acetonitrile–ether gave colorless microcrystals, mp 179–180°, ν_{CO} 1745 cm^{-1}, $\nu_{C=C}$ 1620 cm^{-1}, with nmr absorption in $CDCl_3$ at δ 7.3–8.1 (aromatic multiplet) and 6.45 (methine singlet). Warming the benzoate with 1 g of sodium acetate in chloroform solution afforded 0.25 g of dibenzoylmethylenetriphenylarsenane (VII), mp 208–210°, shown to be identical with an authentic sample by admixture melting point and a comparison of infrared spectra.

B. With Benzoic Anhydride.—A mixture of 0.85 g (2 mmol) of ylide I and 0.45 g (2 mmol) of benzoic anhydride in 20 ml of benzene was stirred overnight. Evaporation of the solvent afforded an oil which crystallized from ether. Recrystallization from benzene–heptane gave 0.5 g (50%) of dibenzoylmethylenetriphenylarsenane (VII), mp 208–210°, ν_{CO} 1520 cm^{-1}, no aliphatic protons were visible in the nmr spectrum. A similar reaction with acetic anhydride gave benzoylacetylmethylenetriphenylarsenane, mp 174°, ν_{CO} 1520 cm^{-1}, with nmr absorption in $CDCl_3$ at δ 7.2–7.8 (area 20.2, aromatic multiplet) and 1.80 (area 3.0, methyl singlet).

Reaction of Ylide I with *p*-Nitrobenzaldehyde.—A solution of 0.85 g (2 mmol) of ylide I with 0.3 g (2 mmol) of *p*-nitrobenzaldehyde in 20 ml of benzene was stirred overnight during which time a yellow precipitate appeared. The precipitate was removed and the filtrate was chromatographed on alumina to afford additional yellow substance. The combined yellow products were crystallized from ethanol to afford 0.5 g (90%) of *p*-nitrobenzalacetophenone (IX), mp 164–165° (lit.[17] mp 160–161°).

Registry No.—I, 24904-06-1; VI, 24904-07-2; bis-(2,4-dinitrophenylhydrazone) of phenyl glyoxal, 4881-22-5.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

(16) G. Maier, *Chem. Ber.*, **95**, 611 (1962).
(17) W. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, **75**, 5990 (1953).

Applications of Nuclear Quadrupole Resonance to Organic Chemistry. II. The Chlorination of Octachlorofulvalene[1a]

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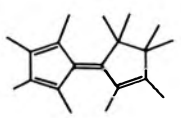
Chlorination of octachlorofulvalene (1) proceeds rapidly at room temperature to give two new $C_{10}Cl_{10}$ isomers: decachloro-2,5-dihydrofulvalene (6) and decachloro-1,2′-dihydrofulvalene (7) in 40 and 15–20% yields, respectively. The structures of these compounds are deduced from their ^{35}Cl nuclear quadrupole resonance (nqr), their ultraviolet spectra, and their chemistry. 6 and 7 rearrange upon heating or under the influence of Lewis acid catalysts to a complex mixture of three other $C_{10}Cl_{10}$ isomers 3, 4, and 5. The same isomeric mixture is obtained under similar conditions from decachloro-1,1′-dihydrofulvalene (2). Structures for 3–5 are proposed on the basis of their nqr and ultraviolet spectra and chemical evidence. Both 6 and 7 also undergo further chlorination: 6 adds chlorine in the absence of light to give a new $C_{10}Cl_{12}$ (50%) and a new $C_{10}Cl_{14}$ (25%) for which the structures 11 and 10, respectively, are suggested; 7, on the other hand, gives the known $C_{10}Cl_{14}$, 13, upon photolytic chlorination.

Recent studies in these laboratories[1b] on various polychlorinated hydrocarbons led to a convenient preparation of octachlorofulvalene[2] (1) in large quantities (Scheme I shows the chlorination of octachlorofulvalene and reactions of $C_{10}Cl_{10}$ isomers.) In the hope that octachlorofulvalene would exhibit interesting properties which might be characteristic of fulvalenes in general, we have undertaken a study of the chemistry of 1. This is the first in a series of papers dealing with that chemistry and is concerned with the chlorination of 1.

Chlorination.—1 reacts very readily with chlorine at room temperature in chloroform solution. The reaction is complete within 1.5–2 hr, as is evidenced by the change in color of the solution from blue to wine red. At least two new compounds 6 and 7, both $C_{10}Cl_{10}$ isomers, are formed in this reaction in 40 and 15–20% yields respectively. However, there are eight different $C_{10}Cl_{10}$ isomers (2–9) which could conceivably arise from chlorination of 1.



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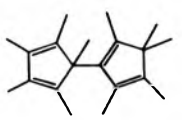

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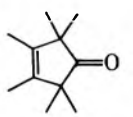
Compound 6 is a deep violet solid, melting at 183–184°. The electronic spectrum of this compound immediately indicates a structure containing the 1,2,3,4-tetrachlorofulvenoid moiety, such as 6 or 8 (compare the spectra of 6 and hexachlorofulvene,[3] Figure 1). Some twisting or stretching of the 1,1′ double bond due to steric repulsions between chlorines in the 2 and 5′ and 5 and 2′ positions would be expected to occur in either 6 or 8, giving rise to the observed bathochromic shift[4] compared with hexachlorofulvene.

The most convincing evidence for the structure proposed for 6 comes from its ^{35}Cl nuclear quadrupole resonance (nqr) spectrum (Table I and Figure 2), which shows only four types of chlorines.[5] A comparison of this spectrum with that of 1, a model for the fulvenoid half of structure 6, allows assignment of the peaks at 36.41 and 37.90 MHz to the chlorines at positions 2′, 3′, 4′, and 5′. The resonance at 37.14 MHz in the spectrum of 6 is comparable with the corresponding low-frequency resonances in the spectra of 1,2,3,3,5,5-hexachlorocyclopenten-4-one (14) and octachlorocyclopentene (15) (models for the chlorinated half of 6). This



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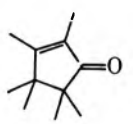

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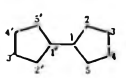
resonance, therefore, can be ascribed to the vinylic chlorines at positions 3 and 4. Finally, the resonances at 38.88 and 39.14 MHz may be assigned to the geminal chlorines at positions 2 and 5 by comparison with the corresponding absorptions in the spectrum of 14. In contrast, 1,2,4,4,5,5-hexachlorocyclopenten-3-one (16), a model for structure 8, shows a very complicated spectrum in both the vinylic and geminal chlorine regions. Thus 6 must have the decachloro-2,5-dihydrofulvalene[2] structure.

The infrared spectrum of 6 further supports this structural assignment with olefinic bands at 1656 (unconjugated double bond) and 1554 cm^{-1} (conjugated double bond). The former band seems especially inconsistent with the alternative structure 8. In addition 6 shows an intense m/e 235 ($C_5Cl_5^+$) peak in its mass spectrum (Table II), which supports the proposed bicyclopentyl carbon skeleton.

(1) (a) Previous paper in this series: A. Roedig, R. Helm, R. West and R. M. Smith, *Tetrahedron Lett.*, 2137 (1969). (b) R. West and D. C. F. Law, unpublished work; D. C. F. Law, Ph.D. Thesis, The University of Wisconsin, 1966.

(2) The IUPAC name for 1 is 2,2′,3,3′,4,4′,5,5′-octachlorobicyclopentadienylidene. To facilitate distinguishing among the numerous $C_{10}Cl_{10}$ isomers presented here without using cumbersome IUPAC nomenclature, yet without resorting to a nondescript tag such as a melting point, we are describing these isomers as fulvalene derivatives and retaining the name fulvalene in preference to bicyclopentadienylidene. The positions of saturation in the $C_{10}Cl_{10}$ isomers are designated using the accepted numbering system.



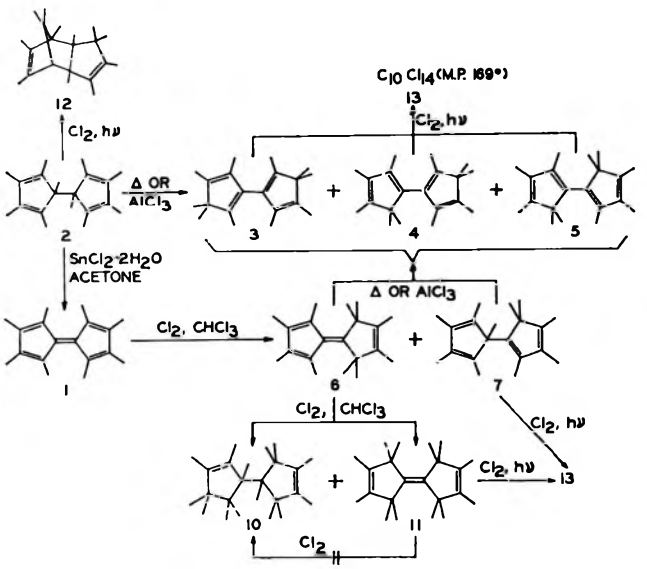
Thus, 5-(1,2,3,3,5,5-hexachlorocyclopenten-4-ylidene)-1,2,3,4-tetrachlorocyclopentadiene (6) is designated decachloro-2,5-dihydrofulvalene; 1-(1,3,-4,5,5-pentachlorocyclopentadien-2-yl)-2,3,4,5,5-pentachlorocyclopentadiene (4) is designated decachloro-2,3′-dihydrofulvalene, etc. Although this system differs from that used by some authors (*e.g.*, see ref 15), we feel that it is significantly easier for the reader to remember.

(3) A. Roedig, *Justus Liebigs Ann. Chem.*, **569**, 161 (1950).

(4) This type of phenomenon is responsible for the large bathochromic shifts exhibited by 1 and octabromofulvalene: R. West and P. T. Kwitowski, *J. Amer. Chem. Soc.*, **90**, 4697 (1968).

(5) Chlorines which are symmetrically equivalent in a given molecule often appear as doublets with splittings of 10–600 kHz due to asymmetric packing in the crystal lattice. For the fundamentals of nqr spectroscopy, see G. Semin and E. I. Fedin in V. I. Gol'danskii, "The Mössbauer Effect and Its Applications in Chemistry," Consultants Bureau, New York, N. Y., 1964, pp 68–119.

SCHEME I

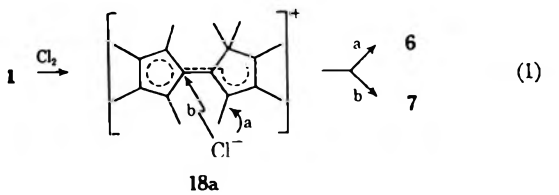


The structure of **6** is confirmed by its isomerization to **5** and by its chlorination, which are discussed below.

The other product, **7**, obtained from chlorination of **1** is a tan to light yellow solid, mp 127–128°. The nqr spectrum of **7** (Table I and Figure 2) establishes the presence of a single tertiary (C-1) chlorine (39.75 MHz; *cf.* the spectrum of **2** which shows two such high-frequency resonances), which narrows the field of possible structures to **7** and **9**. The remainder of the nqr spectrum (ratio of vinylic to geminal chlorines = 7:2) and other spectral data for this compound are also consistent with both structures **7** and **9**. In the infrared olefinic bands are observed at 1618, 1607, and 1568 cm^{-1}, similar to those shown by **2** in this region (1598 and 1568 cm^{-1}).[1] Furthermore, the ultraviolet spectrum of **7** (Table III) is similar to that of hexachlorocyclopentadiene,[6] which confirms the presence of two isolated polychlorocyclopentadienyl fragments in **7**. Finally, the mass spectra of **2** and **7** (Table II) are nearly identical above *m/e* 230. That these two compounds should have similar propensities toward fragmentation and dechlorination would be expected from either of the proposed structures.

The choice between the decachloro-1,2′-dihydrofulvalene[2] (**7**) and the decachloro-1,3′-dihydrofulvalene[2] (**9**) structures rests on the isomerization of this compound to **5** (*vide infra*).

The formation of **6** and **7** in this reaction may be rationalized in the following way. Extended HMO calculations[7] on **1** show that position 2 is the most susceptible to electrophilic attack (assuming an ionic pathway, which seems reasonable under the reaction conditions). Attack by chlorine then gives rise to cation **18a**, followed by nucleophilic attack by chloride ion (predicted[8] to occur predominantly at positions 3, 5 and 1′) at positions 5 and 1′ to give the observed products (eq 1). The lack of 1,2 addition of chlorine (leading here



18a (1)

to **8**) appears fairly general for polychlorinated fulvenes[9] and cyclopentadienes[10] and may be due to steric hindrance by the neighboring *gem*-dichloride group in the intermediate ion (or radical) to further attack by chloride ion (or Cl·).

Isomerization of 6 and 7.—Both **6** and **7** undergo facile rearrangement when heated to slightly above their melting points or when treated with aluminum chloride in chloroform solution at room temperature. Because the thermal and Lewis acid catalyzed isomerizations of decachloro-1,1′-dihydrofulvalene (**2**) were recently reported by Weil[11] to give a mixture of two new $C_{10}Cl_{10}$ isomers, whose structures would have an obvious bearing on the structures of **6** and **7**, we undertook a study of these reactions.[12] During this study a third $C_{10}Cl_{10}$ isomer (**5**) was isolated from this mixture.

Not unexpectedly, the mixtures of $C_{10}Cl_{10}$ isomers obtained from the isomerizations of **2**, **6**, and **7** are identical (by infrared), indicating that complete equilibration has occurred (eq 2). This observation is confirmed by the rearrangement of **3**, **4**, and **5** to the same mixture and by the constancy in composition of the mixture upon prolonged heating. Semiquantitative infrared analysis shows that, at equilibrium, the three isomers (**3**–**5**) are present in the proportions 35–45%:45–55%:5–15% (**3**:**4**:**5**).

$$2 \longrightarrow 3 \rightleftharpoons 4 \rightleftharpoons 5 \begin{matrix} \longleftarrow 6 \\ \longleftarrow 7 \end{matrix} \qquad (2)$$

Compound **3**, isolated by dissolving the reaction mixture in acetic acid and chilling[11] or by trituration and recrystallization from acetonitrile, is a light yellow solid (mp 110–111°). The ultraviolet spectrum of **3** (Table III) indicates a structure with separated, interacting, polychlorocyclopentadienyl fragments (*e.g.*, **2**, whose rings probably interact in a "face-to-face" manner, has similar electronic absorptions Table III).[1] However, the nqr spectrum of this compound (Table I and Figure 3) immediately rules out structures **7** and **9** from consideration. Not only is a structure containing two *gem*-dichloride groups indicated, but the simplicity of the spectrum (showing only three kinds of vinylic chlorines) also excludes the unsymmetrical structure **4**. Both spectra seem comparible only with the decachloro-3,3′-dihydrofulvalene[2] structure (**3**), which contains only cross-conjugation.

Compound **5** is a bright yellow solid melting at 113–114°, which like **4** is isolated from the reaction mixture by chromatography.[10,12] Although the ultraviolet spectrum of **5** (Table III) shows more conjugation than

(6) E. T. McBee, J. D. Idol, Jr., and C. W. Roberts, *J. Amer. Chem. Soc.*, **77**, 4375 (1955).

(7) R. West and R. M. Smith, unpublished results, The University of Wisconsin.

(8) S. Streitwieser, Jr., and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Vol. I, Pergamon Press, Oxford, 1965, p 41.

(9) Hexachlorofulvene, for example, undergoes predominantly 1,4-chlorination under a variety of conditions: Cl_2 at 200° and PCl_5 in CCl_4 at 25°; bubbling Cl_2 through a solution of the fulvene at room temperature, however, has no effect at all.[1]

(10) V. Mark, personal communication.

(11) E. D. Weil, U. S. Patent 3,219,710 (Nov. 23, 1965); *Chem. Abstr.*, **64**, 3377 (1966).

(12) V. Mark and E. D. Weil have also studied these rearrangements in detail to determine product structures, obtaining results in good agreement with ours: V. Mark and E. D. Weil, *J. Org. Chem.*, in press.

TABLE I

^{35}Cl NUCLEAR QUADRUPOLE RESONANCE SPECTRA OF SELECTED CHLOROCARBONS

Compd	T, °K	Vinylic chlorine resonances[a]	Geminal chlorine resonances[a]	Tertiary chlorine resonances[a]
1	298[b]	36.17 (4),[c] 37.19 (2), 37.37 (2)		
	77[d]	36.64 (4), 37.73 (2), 37.84 (2)		
2	298	36.34, 36.69, 37.04, 37.22 (8 complex[e])		38.94 (1), 39.40 (1)
	77	37.12, 37.20, 37.40, 37.56, 37.84, 38.10 (8 complex)		39.35 (1), 39.75 (1)
3	298	36.21 (2), 36.52 (2), 36.73 (2)	38.67 (2), 39.06 (2)	
	77[d]	36.77 (2), 37.02 (2), 37.35 (2)	39.18 (2), 39.56 (2)	
4	298	36.30 (1), 36.48 (1), 36.66 (2), 36.79 (1), 36.88 (1)	38.47 (3 triplet[e]), 38.85 (1)	
	77[d]	36.82 (1), 37.01 (1), 37.09 (1), 37.19 (1), 37.23 (1), 37.42 (1)	38.91 (1), 38.97 (1), 39.03 (1), 39.31 (1)	
5	298	36.1 (2), 36.4 (1), 36.6 (2), 36.8 (1)	38.3 (2 doublet[e]), 38.9 (1), 39.5 (1)	
	77[d]	36.65 (1), 36.92 (1), 37.17 (2), 37.22 (1), 37.26 (1)	38.70 (1), 38.79 (1), 39.49 (1), 40.00 (1)	
6	298	36.41 (2 doublet), 37.14 (2 doublet), 37.90 (2 doublet)	38.88 (2 doublet), 39.14 (2 doublet)	
	77[d]	36.86, 36.93 (2); 37.52, 37.59 (2); 38.21, 38.45 (2)	39.22, 39.39 (2); 39.49, 39.59 (2)	
7	298	36.10 (4 triplet), 36.56 (3 doublet)	39.03 (2)	39.75 (1)
	77	37.02 (4 triplet), 37.41 (3 doublet)	39.77 (2)	40.37 (1)
11	298	37.4 (2), 37.5 (2)	39.0–39.6 (8 complex)	
14	298	37.05 (2)	38.07 (2), 38.42 (2)	
	77	37.83 (2)	39.27 (2), 39.62 (2)	
15	298	36.65 (1), 37.18 (1)	38.72, 39.01, 39.4, 40.36 (6 complex)	
	77	37.51 (1), 38.01 (1)	39.45 (1), 39.70 (1), 39.85 (1), 40.07 (1), 40.28 (1), 41.25 (1)	
16	77	37.33 (1); 37.75, 38.12 (1)	39.23 (1), 39.56 (1); 40.2–40.4 (2 complex)	
17	77[d]	36.40, 36.43, 36.50 (2 complex); 36.84, 36.90, 37.04 (4 complex)	38.29 (1), 38.33 (1)	
C_5Cl_6	77[f]	36.95 (2), 37.28 (1), 37.45 (1)	38.81 (1), 39.08 (1)	

[a] Resonant frequencies measured in MHz. [b] All room temperature and some low temperature spectra were obtained on the Wilks NQR-1; frequencies are accurate to ±0.10 MHz. [c] Numbers in parentheses indicate relative number of chlorines. [d] Spectra obtained on Decca Radar spectrometer; frequencies accurate to ±0.01 MHz. [e] Complex, relative areas under and/or positions of peaks uncertain; doublet, frequency measured at center of two closely spaced peaks; triplet, frequency measured at center of three closely spaced peaks. [f] Hexachlorocyclopentadiene: H. O. Hooper and P. J. Bray, *J. Chem. Phys.*, **33**, 334 (1960).

TABLE II

MASS SPECTRA OF $C_{10}Cl_{10}$ ISOMERS

	Relative intensities[a] of high mass fragments					
Compd	$C_{10}Cl_{10}^{\cdot+}$	$C_{10}Cl_8^{\cdot+}$	$C_{10}Cl_6^{\cdot+}$	$C_{10}Cl_4^{\cdot+}$	$C_5Cl_6^{\cdot+}$	$C_5Cl_5^{+}$
2	<1%	11.3%	24.4%	20.6%	10.1%	100.0%
3	<1%	50.8%	97.3%	76.2%	2.5%	100.0%
4	<1%	70.0%	100.0%	48.2%	13.5%	75.4%
5	<1%	1.4%	2.9%	1.9%	12.0%	100.0%
6	<1%	4.1%	5.5%	4.1%	15.1%	100.0%
7	<1%	13.5%	30.2%	22.6%	6.5%	100.0%

[a] Only the intensities of the first peak (lowest m/e) in each cluster are compared.

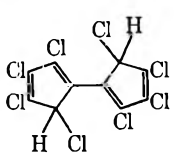
TABLE III

ULTRAVIOLET SPECTRA OF SELECTED CHLOROCARBONS

Compd	λ_{max}, nm (log ϵ)
2[a]	330 (3.47), 280 (3.32)
3	328 (3.39), 274 (3.76)
4	319 (3.60), 228 (sh)
5	355 (3.44), 234 (3.86)
6	512 (2.36), 302 (4.27), 227 (sh)
7	324 (3.57), 228 (sh)
17[a]	380 (3.98), 292 (3.32)
C_5Cl_6[b]	323 (3.17)

[a] Reference 1. [b] Hexachlorocyclopentadiene.[6]

is present in **2**, **3**, **4**, and **7**, it is inconsistent with structures **6** and **8**, which contain the tetrachlorofulvenoid moiety. Similar low energy absorption is observed in **17**,[1] where the highest λ_{max} is seen at 380 nm, indicating that **5** also contains the four double bonds in conjugation. In the case of **5** steric repulsions undoubtedly cause the two rings to be significantly canted, causing the observed hypsochromic shift.



17

The nqr spectrum of decachloro-2,2′-dihydrofulvalene[2] (**5**) (Table I and Figure 3) showing a ratio of six vinylic to four geminal chlorines, also lends support to the proposed structure. The large number of geminal chlorine resonances at first appears anomalous,

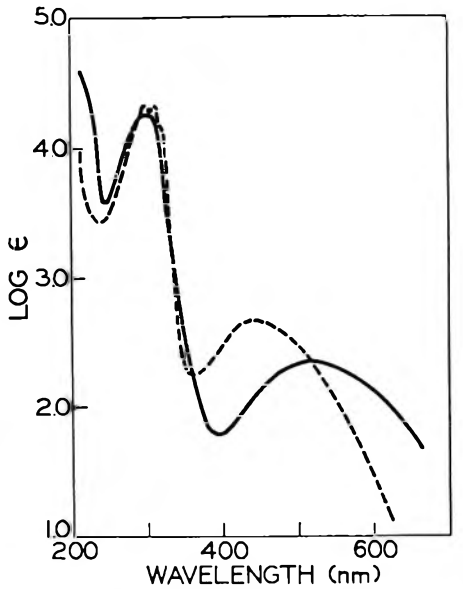


Figure 1.—Electronic spectra of 6 (——) and hexachlorofulvene (- - - - -) in cyclohexane solution.

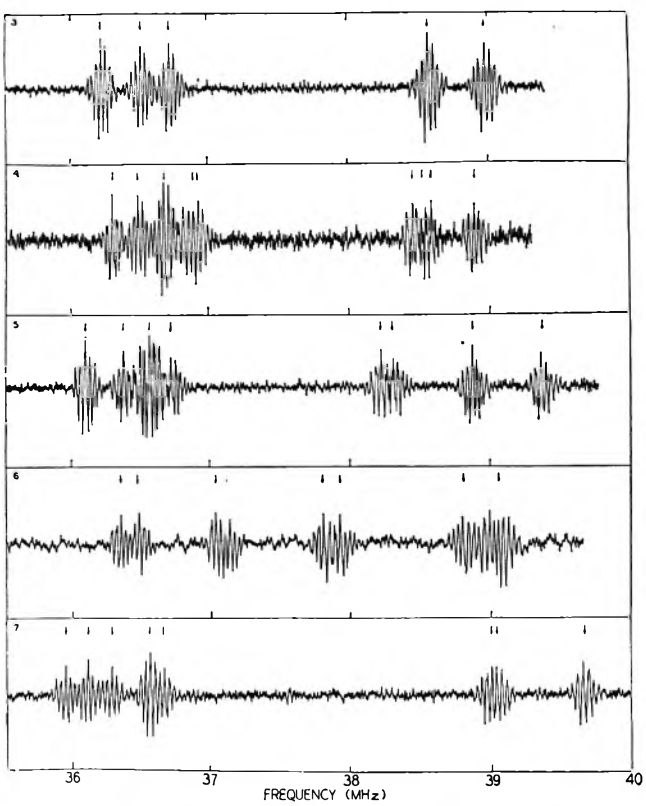
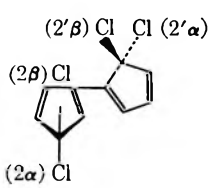


Figure 2.—Nuclear quadrupole resonance spectra of **3**–**7**. Fine structure accompanying each resonance is due solely to the detection system and has no chemical significance.[5]

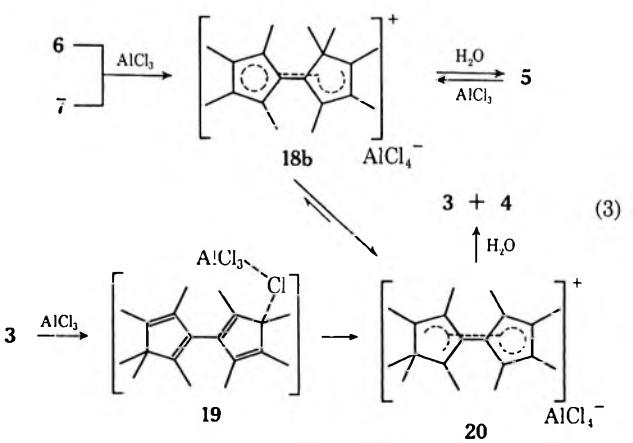
since **5** (like **3**) is a symmetric structure. However, any twisting of the 1,1′ bond induces an inherent nonequivalence to chlorines 2α (2′α) and 2β(2′β), causing first-order splitting; further splitting, however, must be ascribed to asymmetry in the crystal lattice.[5]



The nqr spectrum of **4**, a beige to nearly colorless solid (mp 81–82°), is quite complex, showing ten separate absorptions (ratio of vinylic to geminal chlorines = 6:4) at −196°. This is good evidence in support of the unsymmetrical decachloro-2,3′-dihydrofulvalene[2] structure for this compound. On the other hand, the ultraviolet spectrum of **4** (Table III) is very deceiving, since it is nearly identical with that shown by **7**. Models of **4**, however, indicate that the 2, 5, 2′, and 5′ positions suffer severe steric repulsions in any configuration which even approaches coplanarity of the rings, so that substantial twisting of the 1,1′ bond must occur and effectively isolate the rings.

Also consistent with the proposed structures are the mass spectra of **3**–**5** (Table II). All three compounds give intense $C_5Cl_5^+$ (*m/e* 235) peaks, which is indicative of the bicyclopentyl carbon skeleton. [This fact has been substantiated by the chlorination and catalytic hydrogenation of these compounds[10-12] to the known[13] $C_{10}Cl_{14}$ (mp 169°) (**13**) and bicyclopentyl, respectively.] In addition, **3** and **4** exhibit a definite propensity toward dechlorination, as opposed to fragmentation to $C_5Cl_5^+$. Such behavior seems inconsistent with an alternative structure (**9**) in view of the mass spectral behavior of **2** and **7** (*vide supra*).

If the isomerizations of decachloro-2,5-dihydrofulvalene (**6**) and decachloro-1,2′-dihydrofulvalene (**7**) are followed more closely, the structures of these two compounds can be related to each other and to that of **5**. If **6** is treated with excess aluminum chloride in chloroform solution for a short period of time (2–5 min; 10–24 hr are required for isomerization to the equilibrium mixture) and the reaction is hydrolyzed immediately, a nearly quantitative yield (>90%, by infrared) of **5** results. If **7** is treated similarly, infrared absorption bands due to **5** grow in over those of the starting material in preference to bands due to **3** and **4**. We feel that **6** and **7**, then, give rise to a common intermediate (cation **18b**), which is hydrolyzed exclusively to **5** (eq 3).



(The reaction of **7** is not so clean as that of **6**, however, since the former compound has two nonequivalent sites at which ionization can occur.) **5**, as expected, slowly regenerates **18b** upon treatment with aluminum chloride. The reaction is sluggish, however, and is complicated by some rearrangement, possibly *via* an intermediate in which the migrating chlorine is only weakly

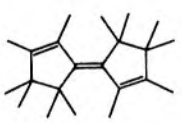
(13) E. T. McBee, J. D. Idol, Jr., and C. W. Roberts, U. S. Patent 2,911,448 (Nov. 3, 1959); *Chem. Abstr.*, **54**, 4527 (1960).

bound to the aluminum chloride.[14] **3**, on the other hand, shows no tendency to form initially the green solution of **18b**, but instead rearranges rapidly *via* the bronze complex **19** and eventually gives what is probably the violet cation **20** in equilibrium with **18b**. Hydrolysis of this mixture of cations (the end product of all the aluminum chloride catalyzed rearrangements) leads to the observed mixture of **3**, **4** and **5**.

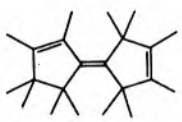
The formation of decachloro-2,2′-dihydrofulvalene (**5**) [instead of the 2,3′ isomer (**4**) which is predicted on steric and electronic[8] grounds to be more favorable] upon hydrolysis of **18b** appears to be kinetically controlled by the extended conjugation present in **5**.[10] This is rather interesting, since cation **18a** (which has a different, and probably more closely associated, counterion) leads to **6** and **7** in a reaction which is also kinetically controlled.

A puzzling question concerning these isomerizations is the relative ratios of the three isomers present at equilibrium. As can be seen from the structures of the compounds obtained, no individual factor controls the isomer distribution. Although **3** suffers least from steric repulsions (the *gem*-dichloride groups are at the "outside" of the molecule), it lacks appreciable conjugation. On the other hand, **5** contains a fair amount of conjugation, but suffers seriously from steric interactions. A happy medium between these opposing factors appears to be reached in **4**.[15]

Chlorination of 6 and 7.—The chlorination of **6** proceeds with relative ease in the absence of light at room temperature in chloroform solution to give two new chlorocarbons, **10** and **11**, in 20–25% and 50% yields, respectively (see Scheme I). **11**, which precipitates from the reaction mixture as a white solid $C_{10}Cl_{12}$ (mp 227–228°), shows only a shoulder at 265 nm (log ϵ ~3.6) in the ultraviolet above 240 nm. This evidence excludes structures having the tetrachlorofulvenoid or even the polychlorocyclopentadienyl fragment of **6** still intact (both have λ_{max} >300 nm). Not so easily excluded, however, are structures **21** and **22**.



21



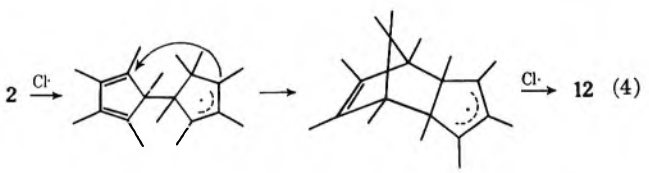
22

A comparison of the ultraviolet spectrum of octachloro-1,3,5-hexatriene [λ_{max} 260–265 nm (shoulder, log ϵ ~3.85)[16]] with that of this compound offers evidence against structure **21**, which would be expected to give rise to a bathochromic shift over the corresponding absorption of its acyclic analog.[17] In choosing between structures **11** and **22**, however, the ultraviolet evidence becomes ambiguous, since the contribution of the numerous steric factors involved here are unknown. However, the nqr spectrum of this compound (Table I) shows a closely spaced doublet in the vinylic chlorine region, which seems consistent only with the more symmetrical structure **11** (*cf.* the spectra of **14** and **16**, Table I). This structure, it must be noted, is consistent with the proposed structure of the starting material **6** (since **8** would be expected to give rise to **11** under the relatively mild reaction conditions) and with the observed predominance of 1,4- over 1,2-chlorination of the fulvene system (*vide supra*).

The mass spectrum of **11** indicates the unrearranged carbon skeleton to be present, showing major peaks at *m/e* 400 ($C_{10}Cl_8 \cdot^+$), *m/e* 330 ($C_{10}Cl_6 \cdot^+$), and *m/e* 260 ($C_{10}Cl_4 \cdot^+$) and a base peak at *m/e* 235 ($C_5Cl_5^+$). The chlorination of **11** under mild conditions to **13**, which is known to have the bicyclopentyl skeleton,[13,18] also confirms this point.

From the chloroform solution obtained in the chlorination of **6** one can isolate **10**, a white solid $C_{10}Cl_{14}$ (mp 186–187°). This compound shows only one ultraviolet absorption [230 nm (log ϵ 4.28)] whose position and intensity are consistent with two isolated double bonds. Preliminary considerations indicate that structure **10** is correct for this compound, since (1) it is compatible with the fact that **11** does not chlorinate to **10** under any conditions, (2) it is consistent with the structure of **6** and could be formed *via* the less favorable **22**, and (3) it contains two heptachlorocyclopentenyl fragments, which is consistent with the resistance of the latter system to further chlorination.[19] However, this structure, like that of **11**, must be considered only tentative.

The chlorination of **7** under light-induced conditions leads to **13**, although the intermediate $C_{10}Cl_{12}$ is not isolated here as it was in the case of **6**. This reaction is also consistent with the structure assigned to **7**. Decachloro-1,1′-dihydrofulvalene (**2**) chlorinates under identical conditions to give **12**,[6] which has a condensed carbon skeleton,[20] by means of proposed mechanism 4.



(14) Similar complex formation followed by ionization, giving rise to a series of color changes, occurs in the reaction of hexachlorocyclopentadiene with $AlCl_3$: P. T. Kwitowski, Ph.D. Thesis, The University of Wisconsin, 1966.

(15) This product distribution is to be contrasted with that obtained in the thermal isomerization of 1,1′-dihydrofulvalene, the hydrocarbon analog of **2**. In that case the only product which is isolated is 2,2′-dihydrofulvalene, the analog of **5**, and conjugative effects can be invoked exclusively to account for the product ratio: E. Hedaya, D. W. McNeil, P. Schissel, and D. J. McAdoo, *J. Amer. Chem. Soc.*, **90**, 5284 (1968).

(16) A. Roedig, G. Voss and E. Kuchinke, *Justus Liebigs Ann. Chem.*, **580**, 24 (1953).

(17) R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 1123 (1941); **64**, 72, 76 (1942).

(18) The formation of **13** from **11** under relatively mild conditions indicates that these two compounds may be structurally related. However, the fact that **13** occurs as the product of so many of these reactions indicates that it also might be the thermodynamic sink for a series of labile $C_{10}Cl_{14}$ isomers. Unfortunately no data is available at present to help solve this problem, so that i, a likely structure for this compound, must be considered tentative at best.

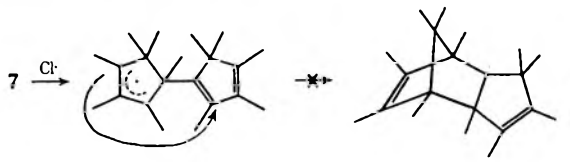
i

(19) J. A. Kritinsky and R. W. Bost, *J. Amer. Chem. Soc.*, **69**, 1918 (1947).

(20) V. Mark has suggested the structure ii for compound **12**. However, a mechanism analogous to that given here must be postulated for the formation of ii from **2**, so that our argument remains unchanged. See ref 12.

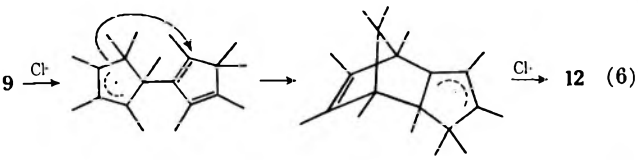
ii

Now **3**, **4** and **5** cannot undergo this type of condensation and, in fact, do not[11,12] (*vide supra*). **7** cannot do this either with any facility (eq 5), but structure **9** (the



(5)

alternative to **7**) presumably could (eq 6). Since *both*



(6)

compounds **7** and **9** are not available, however, their relative behavior in this reaction is unknown; furthermore, the stabilities of the starting materials to the reaction conditions are questionable, so that the above argument is only indicative.

In contrast to the facile electrophilic addition of chlorine to octachlorofulvalene, this compound also exhibits interesting electron-deficient properties. These properties will be the subject of further communications on the chemistry of **1**.

Experimental Section

Decachloro-1,1′-dihydrofulvalene (**2**) was prepared from commercial grade hexachlorocyclopentadiene according to the method of McBee and coworkers,[6] mp 122–123° (lit.[6] 122–122.5°).

The infrared spectra of pure solids were obtained on a Perkin-Elmer 237 spectrometer as mulls with mineral oil (Nujol) between sodium chloride disks. Ultraviolet spectra were taken on a Cary Model 14 recording spectrophotometer in 2-cm and/or 0.5-mm quartz cells, using Spectrograde cyclohexane as solvent unless otherwise indicated. Mass spectra were recorded on the CEC 21-103C spectrometer, equipped with heated inlet, and the AEI MS-902 high resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preliminary nqr spectra were run on the Wilks NQR-1 commercial spectrometer with superregenerative oscillating detector, using a Hewlett–Packard Model 524B electronic counter to measure frequencies. Wherever the center of the envelope due to a single peak was obvious, the frequency at that point was measured with an accuracy of ±0.10 MHz. In cases where the center was not obvious owing to overlapping peaks, the frequency of the approximate center of that group of peaks was measured to the same degree of accuracy. A number of low temperature spectra were run on the Decca Radar commercial spectrometer with superregenerative oscillating detector and side band suppressor (which facilitated the location of individual peaks); these spectra are noted in Table I. The spectra which are reproduced in this paper were obtained on the Wilks NQR-1A commercial spectrometer. Samples that were solid at room temperature were slowly recrystallized from pentane to afford crystals as large as possible; sample sizes varied from 0.5–3.0 g. Liquid samples were slowly cooled to −20 or −80° before immersion in liquid nitrogen for low temperature spectra. Commercial grade octachlorocyclopentene and 1,2,4,4,5,5-hexachlorocyclopenten-3-one were used for nqr analysis, but 1,2,3,3,5,5-hexachlorocyclopenten-4-one was prepared by the method of McBee, *et al.*,[21] mp 87–89° (lit.[21] 91–92°).

Octachlorofulvalene (1).[1]—A solution of 12 g of tin(II) chloride dihydrate (0.053 mol) in 75 ml acetone was added dropwise to decachloro-1,1′-dihydrofulvalene[6] (25 g, 0.053 mol), dissolved in 375 ml of refluxing acetone, over a period of 20–25 min with constant, vigorous stirring. The reaction mixture became green almost immediately. After an additional 5–10 min of refluxing, the contents of the flask were cooled to room temperature, and stirring was stopped. Decantation of the reaction solution uncovered 12.0 g (56.5%) of octachlorofulvalene, which was washed with small portions of acetone and air-dried. Recrystallization from hexane with activated charcoal yielded **1** as shiny, metallic-blue prisms (7.7 g, 36.1%), mp 200° dec (lit.[1,22] 200° dec). **1** is stored most conveniently at room temperature in a vacuum desiccator, as it appears to undergo slow oxidation in the air.

Chlorination of 1.—Octachlorofulvalene, 20.0 g (0.050 mol), was placed in a 3-l., round-bottom flask, and 2500 ml of chloroform was added. Chlorine was admitted at a moderate rate (1–3 cc/sec) to the solution at room temperature *via* a gas dispersion tube while the solution was vigorously stirred. After 1.5–2 hr the color of the solution had changed from deep blue to wine red, at which time chlorine admission was stopped. The solvent was blown off under nitrogen over a period of 24 hr, leaving a black, gummy solid. Recrystallization of this solid from 1400 ml of acetone (four crops) gave 8.7 g (37.5%) of decachloro-2,5-dihydrofulvalene (**6**). A second recrystallization from hexane yielded a pure sample of **6** as violet prisms, mp 183–184°. *Anal.* Calcd for $C_{10}Cl_{10}$: C, 25.30; H, 0.00; Cl, 74.70. Found: C, 24.90; H, 0.05; Cl, 75.01. Although the mass spectrum of **6** shows no molecular ion peak (*m/e* 470), it does show a fairly intense peak at *m/e* 400. Calcd intensities for 8 Cl:[23] M + 2, 261%; M + 4, 298%; M + 6, 194%; M + 8 79.3%. Observed intensities: M + 2, 255%; M + 4, 278% M + 6, 174%; M + 8, 85.5%. Other important fragments in this spectrum appear in Table II. Ir: ν_{max}^{mull} 1656 (s), 1554 (m), 1275 (s), 1258 (s), 1203 (m), 1190 (m), 1093 (m), 990 (s), 944 (m), 875 (m), 845 (w), 806 (s), 757 (m), 726 (w), 680 (m), and 671 cm^{-1} (m). Uv: $\lambda_{max}^{cyclohexane}$ 512 nm (log ε 2.36), 302 nm (4.27), and 227 nm (shoulder).

The filtrate remaining after recrystallization of **6** was taken to dryness, and the remaining solid was recrystallized from acetonitrile with decolorizing charcoal. Two crops of crystals were obtained: 3.0 g (13%) of decachloro-1,2′-dihydrofulvalene (**7**) as beige needles, mp 127–128°. *Anal.* Calcd for $C_{10}Cl_{10}$: C, 25.30; H, 0.00; Cl, 74.70. Found: C, 25.41; H, 0.05; Cl, 74.84. The mass spectrum of **7** shows a small, but visible, molecular ion peak at *m/e* 470. The first peak of major intensity, however, occurs at *m/e* 400. Calcd intensities for 8 Cl:[23] M + 2, 261%; M + 4, 298%; M + 6, 194%; M + 8, 79.3%. Observed intensities: M + 2, 252%; M + 4, 280%; M + 6, 178%; M + 8, 70.0%. Ir: ν_{max}^{mull} 1618 (m), 1607 (s), 1568 (m), 1260 (w), 1233 (s), 1225 (s), 1163 (m), 1007 (m), 970 (w), 954 (w), 940 (m), 846 (m), 800 (s), 725 (m), 719 (m), 670 (s), and 658 cm^{-1} (s). Uv: $\lambda_{max}^{cyclohexane}$ 324 nm (log ε 3.57) and 228 nm (shoulder).

Chlorination of 6.—Decachloro-2,5-dihydrofulvalene (**6**), 2.05 g (4.3 mmol), was chlorinated in 150 ml chloroform at room temperature. Vigorous stirring was maintained, and the reaction vessel was shielded from light with aluminum foil. After 24 hr the reaction solution had become yellow, and an off-white precipitate had formed. The solution was reduced to half-volume, and the solid was filtered off, 1.15 g (50%) of **11**. Recrystallization from chloroform with decolorizing charcoal produced **11** as fluffy, white needles, mp 227–228°. *Anal.* Calcd for $C_{10}Cl_{12}$: C, 22.02; H, 0.00; Cl, 77.98. Found: C, 21.91; H, 0.06; Cl, 78.19. **11** showed a small molecular ion peak at *m/e* 540, as well as small fragment ion clusters at *m/e* 505 ($C_{10}Cl_{11}^+$), *m/e* 470 ($C_{10}Cl_{10}\cdot^+$), *m/e* 435 ($C_{10}Cl_9^+$), but the first peak of major intensity again occurred at *m/e* 400. Calcd intensities for 8 Cl:[23] M + 2, 261%; M + 4, 298%; M + 6, 194%; and M + 8, 79.3%. Observed intensities: M + 2, 254%; M + 4, 288%; M + 6, 165%; and M + 8, 86.1%. Ir: ν_{max}^{mull} 1658 (m), 1650 (s), 1626 (w), 1197 (s), 1125 (w), 1045 (s), 1000 (m), 928 (m), 886 (m), 871 (s), 775 (s), 740 (m), 724 (m), and 645 cm^{-1} (s). Uv: $\lambda_{max}^{CHCl_3}$ 265 nm (shoulder, log ε 3.61).

Taking the reaction solution to dryness yielded a colorless oil that, upon standing, solidified to give 0.6 g (23%) of **10**. Recrystallization from acetone led to **10** as fluffy, white needles, mp 186–187°. *Anal.* Calcd for $C_{10}Cl_{14}$: C, 19.79; H, 0.00;

(21) E. T. McBee, D. L. Crain, R. D. Crain, L. R. Belohlav, and H. P. Braendlin, *J. Amer. Chem. Soc.*, **84**, 3557 (1962).

(22) V. Mark, *Tetrahedron Lett.*, 333 (1961).

(23) J. H. Beynon, "Mass Spectrometry and Its Applications to Organic Chemistry," Elsevier, Amsterdam, 1960, p 298.

Cl, 80.21. Found: C, 19.65; H, 0.00; Cl, 80.62. Ir: ν_{max}^{mull} 1622 (m), 1573 (m), 1228 (m), 1180 (s), 1143 (m), 110 (w), 1054 (m), 1025 (m), 950 (w), 900 (m), 877 (m), 849 (m), 823 (m), 806 (w), 760 (s), 750 (s), 712 (w), 688 (m), and 663 cm^{-1} (m). Uv: $\lambda_{max}^{cyclohexane}$ 230 nm (log ϵ 4.24).

Chlorination of 7.—A solution of 0.93 g (2.0 mmol) of decachloro-1,2′-dihydrofulvalene (**7**) in 125 ml of carbon tetrachloride was chlorinated using a gas dispersion tube for 20 hr. The reaction flask was irradiated during the reaction with a mercury vapor lamp, and a reflux condensor was utilized to minimize solvent loss. Upon completion of the reaction the solvent and excess chlorine were evaporated, and a colorless oil, which subsequently solidified, was obtained, **13** (1.25 g, >100%). Recrystallization of this solid from pentane gave 0.90 g (75%) of **13** as colorless needles, mp 166–167° (lit.[13] 168–169°). The infrared spectrum of this compound was superimposable upon that of **13** prepared by chlorination of **3**,[11] and a mixture of these compounds showed no melting point depression.

Chlorination of 11. A. In the Absence of Light.—A suspension of 0.55 g of **11** (1.0 mmol) in 150 ml of chloroform was stirred vigorously for 48 hr, while chlorine was admitted *via* gas dispersion tube. The reaction flask was covered to exclude light. The solvent then was reduced to one-fourth of its original volume, and the existing precipitate was isolated and air-dried to give 0.45 g (82%) of unchanged **11**, as shown by infrared.[24]

B. In Diffuse Room Light.—**11** (0.50 g, 0.9 mmol) was placed in 150 ml of chloroform, and this suspension was chlorinated for 24 hr. In this case, light from the room was allowed to enter the reaction flask, although no ultraviolet irradiation was used. A clear, yellow solution resulted, which, after solvent removal, gave crystals of **13**. These crystals were washed with acetone and isolated to give 0.2 g (32%) of **13**. Recrystallization from pentane gave **13** as colorless needles, mp 162–166° (lit.[13] 168–169°). This product was shown to be identical by infrared spectroscopy and mixture melting point with **13** prepared by chlorination of **3**.[11]

Thermal Rearrangement of 2.[11,12]—Decachloro-1,1′-dihydrofulvalene (**2**), 15.0 g (0.032 mol), was placed in a pyrex tube that was flushed with nitrogen and kept under a positive nitrogen pressure during the entire reaction. The tube was heated at 128–130° for 40 hr with an oil bath. At this point the yellow oil that had formed showed no signs of starting material, as evidenced by the disappearance of bands at 1568 and 1250 cm^{-1} in the infrared. This oil, after cooling, was partially dissolved in 35 ml glacial acetic acid, and the resulting suspension was cooled for 3–4 hr in a refrigerator. The precipitate that had formed was filtered off and air-dried to give 5.30 g (34%) of decachloro-3,3′-dihydrofulvalene (**3**). Recrystallization from acetonitrile produced small, light yellow plates of **3**, mp 109–110° (lit.[11] 110–111°). The infrared and ultraviolet spectra of this compound were identical with those reported in the literature.[11,12]

The acetic acid filtrate, after isolation of **3**, was diluted with 150 ml of water, causing the chlorocarbon layer to oil out. The organic materials were extracted into dichloromethane, and this solution was washed with water and dried over anhydrous calcium chloride. Evaporation of the solvent led to an oil, which was placed on a 3.5 ft × 3/4 in. column of neutral aluminum oxide and eluted with pentane. Initial fractions, analyzed by infrared, contained significant amounts of **3**, whereas middle fractions were composed mostly of decachloro-2,3′-dihydrofulvalene (**4**). The final fractions, on the other hand, were predominantly decachloro-2,2′-dihydrofulvalene (**5**). The intermediate fractions were resubjected to chromatography (aluminum oxide–pentane) to give 0.5 g (3.3%) of pure **4** as a nearly colorless powder, mp 80–81.5° (lit.[11] 81–82°). The infrared spectrum of this compound was identical with that of a pure sample of **4**.[25]

Thermal Rearrangement of Other $C_{10}Cl_{10}$ Isomers.—0.5 g samples of **3**, **5**, **6**, and **7** were placed in Pyrex tubes and heated at 130–140° until constant infrared spectra were obtained. The times required for these reactions were as follows: **3**, 2–2.5 hr; **5**, 1.5–2 hr; **6**, 36–48 hr (this reaction is accompanied by some oxidation and proceeds much more rapidly above the melting point of **6**); and **7**, 10–20 hr. The infrared spectra of the oils obtained from these reactions were literally superimposable upon one another and upon that obtained from the thermal rearrangement of **2**.

Aluminum Chloride Catalyzed Rearrangement of $C_{10}Cl_{10}$ Isomers.—Samples (0.5–1.0 g) of **2**, **3**, **5**, **6**, and **7** were stirred with 0.25–0.50 g of anhydrous aluminum chloride (~1.75 mol $AlCl_3$)/mol of substrate) in 10–20 ml of chloroform at room temperature for varying lengths of time: **2**, 12–16 hr;[26] **3**, 3–6 hr; **5**, 3–6 hr; **6**, 16–24 hr; and **7**, 3–7 hr. The mixtures were hydrolyzed by addition of 25–50 ml of water. The organic layers were diluted with chloroform, separated, washed with water, and dried over anhydrous calcium chloride. Removing the solvent on a rotary evaporator produced oils similar to those obtained in the thermal isomerizations. The infrared spectra of these oils were superimposable upon one another and upon those obtained in the thermal rearangements.

Aluminum Chloride Catalyzed Rearrangement of 6 at Short Reaction Times.—Decachloro-2,5-dihydrofulvalene (**6**) (1.35 g, 2.8 mmol) and anhydrous aluminum chloride (0.65 g, 4.7 mmol) were stirred vigorously in 10–15 ml of chloroform at room temperature. After 2–5 min, the color of the solution had changed from violet to yellow to deep green. When the green color had persisted for 1 min, 10–15 ml water was added with stirring. The organic layer was diluted with chloroform, washed with water, and dried over anhydrous calcium chloride. Evaporation of the solvent led to a viscous oil which solidified upon trituration with acetonitrile to give 1.30 g (96%) of decachloro-2,2′-dihydrofulvalene (**5**). The crude product was recrystallized from acetonitrile to give 0.75 g (60%) of **5** as bright yellow clusters, mp 113–114°. *Anal.* Calcd for $C_{10}Cl_{10}$: C, 25.30, H, 0.00; Cl, 74.70. Found: C, 25.13; H, 0.10; Cl, 74.50. The mass spectrum of **5** shows no appreciable peaks above *m/e* 420, but exhibits an intense peak at *m/e* 400. Calcd intensities for **8** Cl:[23] M + 2, 261%; M + 4, 298%; M + 6, 194%; M + 8, 79.3%. Observed intensities: M + 2, 254%; M + 4, 287%; M + 6, 183%; M + 8, 79.2%. Ir: ν_{max}^{mull} 1600 (s), 1543 (m), 1277 (w), 1230 (s), 1175 (w), 1156 (s), 992 (w), 965 (m), 902 (m), 805 (s), 725 (m), 699 (m), and 662 cm^{-1} (m). Uv: $\lambda_{max}^{cyclohexane}$ 355 nm (log ϵ 3.44) and 234 nm (3.86). This compound was shown by infrared and mixed melting point to be identical with **5** obtained in low yield from the equilibrium mixture of $C_{10}Cl_{10}$ isomers.

Aluminum Chloride Catalyzed Rearrangement of 7 at Short Reaction Times.—0.4 g (0.8 mmol) of decachloro-1,2′-dihydrofulvalene (**7**) was dissolved in 5 ml chloroform, and 0.2 g (1.4 mmol) of anhydrous aluminum chloride was added. After stirring this suspension vigorously for 4–6 min at room temperature, the color became dark yellow, then green. Hydrolytic work-up, as before, led to an oil whose infrared spectrum showed mainly bands due to the starting material. Also present, however, were new bands at 1543, 1277, 992 and 699 cm^{-1}; these bands are unique for **5** and were superimposable upon the corresponding peaks in the infrared spectrum of pure **5**. Noticeably less intense, on the other hand, were bands at 1645–1640, 1303–1299 and 1030 cm^{-1}, which are unique for **3** and **4**.

Registry No.—**1**, 24807-57-6; **2**, 24807-58-7; **3**, 24807-59-8; **4**, 24807-60-1; **5**, 24807-61-2; **6**, 24807-05-4; **7**, 24807-06-5; **10**, 24807-07-6; **11**, 24854-63-5; **14**, 24807-08-7; **15**, 559-40-0; **16**, 24807-10-1; **17**, 24807-11-2; hexachlorocyclopentadiene, 77-47-4.

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(24) In working up the reaction solution small amounts of a new chlorocarbon (mp ~125°, presumably a $C_{10}Cl_{14}$) were found. These results were not reproducible, but do emphasize the lack of structural relationship between **11** and **10**.

(25) We wish to thank Dr. Mark for a sample of **4** and for experimental details for isolating **4** from the isomer mixture.

(26) The rearrangement of **2** must be carried out in refluxing chloroform.

The Pyrolysis of Nopinone[1a]

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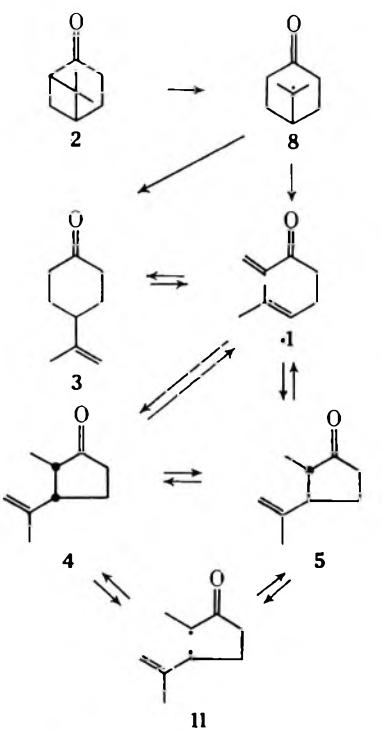
Vapor-phase pyrolysis of nopinone in the range 460–600° yields 7-methylocta-1,6-dien-3-one (**1**), 4-isopropenylcyclohexanone (**3**), and *cis*- and *trans*-2-methyl-3-isopropenylcyclopentanone (**4** and **5**). In the same temperature range, dienone **1** gives **4** and **5**, and **4** and **5** interconvert. The attempted photocyclization of dienone **1** was not successful. The details and mechanisms of these reactions are discussed.

In the course of studies on photochemical ring closures,[2] we required 7-methylocta-1,6-dien-3-one (**1**) as a potential precursor of the bicyclo[3.1.1]heptane nucleus with the usual terpene substitution pattern. Since vapor-phase pyrolysis of β-pinene has been reported to yield predominately β-myrcene,[3] the pyrolysis of nopinone (**2**) was examined as a synthetic route to **1**. In fact, vapor-phase thermolysis of bicyclic ketone **2** using a flow unit at 460–600° and reduced pressure did result in the desired acyclic ketone. However, the synthetic utility of this process was diminished by the observation that substantial quantities of three additional materials were found in the pyrolysis product. These were identified as 4-isopropenylcyclohexanone (**3**), *cis*-2-methyl-3-isopropenylcyclopentanone (**4**), and *trans*-2-methyl-3-isopropenylcyclopentanone (**5**). The relative proportions of the products was a function of both the temperature and the rate of passage through the thermal zone, but a typical run at 600° gave 39% **1**, 27% **3**, 14% **4**, 8% **5**, and 11% total of a number of unidentified minor products. Conditions were not achieved which caused substantial conversion of **1** to **2** without the concurrent formation of large amounts of the other products.

The mass spectra of each of the pyrolysis products display a molecular ion at *m/e* 138 demonstrating their isomeric relationship to nopinone. The spectral properties of these compounds which are detailed in the Experimental Section fully support the assigned structures. Carbonyl absorption in the ir was particularly instructive in differentiating among cyclopentanone, cyclohexanone, and conjugated acyclic ketone functions. Distinction between epimeric cylcopentanones **4** and **5** was based on the chemical shifts of the methyl group attached to C_2. These values are δ 0.82 and 0.95 for **4** and **5**, respectively, and reveal a significant high field shift for **4**. This is in accord with the molecular geometry of **4** which positions the saturated methyl group in the shielding zone above the plane of the isopropenyl double bond.[4] Chemical confirmation of this assignment is provided by base isomerization which generates a mixture from either epimer in which the *trans* compound predominates.

Examination of the behavior of the pyrolysis products to the reaction conditions afforded insight into the nature of the thermal transformations of **2**. At 570° acyclic dienone **1** was substantially (70%) converted to the isomeric cyclopentanones **4** and **5** along with a small amount of cyclohexanone **3**. At this temperature **3** underwent only 10% transformation mainly to the isomeric cyclopentanones. Even at 740° less than half of **3** was converted to products. The major reaction of **4** and **5** was interconversion, and at 740° the same 1:6 ratio of **4** and **5** was obtained from either isomer.



The thermal isomerization of nopinone finds close analogy in the pyrolytic behavior of the related hydrocarbon β-pinene which is converted to β-myrcene and lesser quantities of limonene and 4-isopropenylmethylenecyclohexane.[3] A diradical mechanism has been suggested for the hydrocarbon isomerization, and the appropriate modification is an attractive explanation for the origin of acyclic dienone **1** and cyclohexanone **3** in the pyrolysis of **2**. This description is also in accord with other observations on the thermal reaction of cyclobutanes.[5] The pyrolysis of tricyclic compound **6** which gives bicyclic ketone **7** is especially relevant as an example in which hydrogen atom abstraction interrupts the cyclobutane fission process.[6]

(1) (a) Supported by the Public Health Service (Grant GM 12860). (b) Alfred P. Sloan Research Fellow, 1968–1970.

(2) J. K. Crandall and C. F. Mayer, *J. Amer. Chem. Soc.*, **89**, 4374 (1967).

(3) D. V. Banthrope and D. Whittaker, *Quart. Rev.* (London), **20**, 373 (1966).

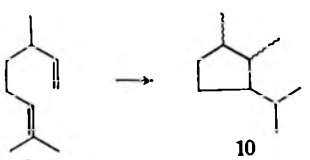
(4) D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists," Academic Press, New York, N. Y., 1967, p 110.

(5) H. M. Frey, *Advan. Phys. Org. Chem.*, **4**, 147 (1966).

(6) C. H. Heathcock and B. E. Ratcliffe, *J. Org. Chem.*, **33**, 3650 (1968).

Cleavage of the indicated cyclobutane bond of nopinone yields diradical **8**, the most stable such species derivable from **2**. Other modes of bond homolysis must sacrifice either the α-keto radical[7] or the tertiary radical site, and this fact is apparently reflected in the transition state energies for the alternate reaction pathways. Diradical **8** can subsequently cleave the central bond of the 1,4-diradical moiety to yield **1**, or it can undergo intramolecular disporportionation by a 1,5-hydrogen atom transfer to produce cyclohexanone **3**. The latter could also arise by a 1,7-hydrogen shift to give the enol of **3** as an intermediate. Such a 1,7 transfer apparently operates in the case of β-pinene.[3]

The conversion of **1** to cyclopentanones is closely analogous to the known thermal rearrangement of 3,7-dimethyl-1,6-octadiene (**9**) to the isomeric 1,2-dimethyl-3-isopropenylcyclopentanes (**10**) and related examples.[8] These transformations are intramolecular versions of the ene reaction which appears to occur by a concerted cycloaddition mechanism in those instances where this point has been examined.[9]



9 10

The interconversion of cyclopentanones **4** and **5** may involve homolytic cleavage of the C_2–C_3 bond of the cyclopentane ring to give diradical **11**, which can undergo reclosure to either epimer. On the other hand, the presence of a trace of dienone **1** among the pyrolysis products from each of these suggests the alternate, and perhaps more likely, possibility of interconversion through **1** by a combination of ene and reverse ene reactions.

Attempts to reverse photochemically the **2** to **1** conversion were without success. A variety of direct or sensitized irradiation experiments did not yield volatile products, although transformation of **1** to polymer was observed. Similar resistance to photocyclization has been found for the parent 1,6-heptadien-3-one and for 1,3,6-heptatriene.[10] Recent evidence suggests that 1,6-dienes should preferentially cyclize to bicyclo[3.2.0]heptane skeletons rather than the desired bicyclo[3.1.1]heptanes,[11] although the latter has been observed when the 1,6-diene is restricted in geometry by a medium-ring environment.[12] Nonetheless, neither mode of cyclization has been observed in the present studies, suggesting that 1,6-dienes are, in general, less prone to cycloaddition than 1,5-dienes.[13]

(7) There appears to be some question about the amount of stabilization offered by a carbonyl group adjacent to a radical center, but an acyl group is probably equivalent to an alkyl substituent at the minimum. See ref 5, p 176.

(8) W. D. Huntsman, V. C. Solomon, and D. Eros, *J. Amer. Chem. Soc.*, **80**, 5455 (1958), and references therein.

(9) For example, see J. A. Berson, R. G. Wall, and H. D. Perlmutter, *ibid.*, **88**, 187 (1966); R. K. Hill and M. Rabinovitz, *ibid.*, **86**, 965 (1964); H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

(10) Unpublished results, J. K. Crandall.

(11) R. Srinivasan and K. H. Carlough, *J. Amer. Chem. Soc.*, **89**, 4932 (1967); M. Brown, *J. Org. Chem.*, **33**, 162 (1968); L. Crombie, R. Ponsford, A. Shani, B. Yagnitinsky, and R. Mechoulam, *Tetrahedron Lett.*, 5771 (1968); J. R. Scheffer and M. C. Lungle, *ibid.*, 845 (1969); J. W. Stankorb and K. Conrow, *ibid.*, 2395 (1969).

(12) C. H. Heathcock and R. A. Badger, *Chem. Commun.*, 1510 (1968).

(13) F. T. Bond, H. L. Jones, and L. Scerbo, *Tetrahedron Lett.*, 4685 (1965). See also W. L. Dilling, *Chem. Rev.*, **69**, 845 (1969); **66**, 373 (1966).

Experimental Section

General.—Nuclear magnetic resonance spectra (nmr) were recorded on a Varian A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard. Mass spectra were determined using an AEI MS-9 mass spectrometer at 70 eV. Gas-liquid partition chromatography (glpc) was carried out on a Varian-Aerograph Series 1200 chromatograph (analytical, flame ionization detector) using an 8 ft × $^1/_8$ in. 15% Carbowax 20M on 60–80 Chromosorb W column and on an Aerograph A-90P-3 chromatograph (preparative) using a 10 ft × $^3/_8$ in. 30% XF-1150 on 45–60 Chromosorb W or a 10 ft × $^3/_8$ in. 30% FFAP on 60–80 Chromosorb W column. Percentage composition data were estimated by integrated peak areas. Analyses were performed by Midwest Microlab, Inc.

General Pyrolysis Procedure.—The vapor-phase pyrolysis apparatus consisted of a horizontal Pyrex or fused-quartz tube, 10-mm i.d., inserted through an E. H. Sargent and Co. tube furnace 170 mm in length. The Pyrex tube was packed with Pyrex helices, 0.25-in. o.d. The quartz tube was used unpacked or was packed with quartz chips 1 mm thick, other dimensions variant. Samples were placed in a flask attached at one end of the tube and the vapors were condensed in a Dry Ice trap at the other end. A pressure of less than 1 mm was maintained by a vacuum pump attached at the trap. The throughput could be increased by heating the sample with an infrared lamp.

Nopinone (2).—A modification of the ozonolysis method of Conia and Leriverend[14] was used. The output from a Welsbach Model T-408 ozonator was bubbled through a solution of 25 g of β-pinene and 30 ml of pyridine in 150 ml of methylene chloride at −78° for 6 hr. The brown solution was purged with oxygen for 30 min, allowed to warm to room temperature, and washed with four 50-ml portions of 10% hydrochloric acid. After washing with water, the solution was dried and concentrated, and the residue was distilled to give 11.2 g (44%) of **2**: bp 55–60° (2 mm); ir 5.83 μ; nmr δ 2.2 (m, 8), 1.31 (s, 3), and 0.81 (s, 3).

Pyrolysis of Nopinone.—A 5-g sample of nopinone was passed through the packed quartz tube at 600° in 4 hr with the aid of the infrared lamp. Glpc assay indicated that the 4.53 g (90%) of yellow liquid collected in the trap consisted of 39% 7-methylocta-1,6-dien-3-one (**1**), 27% 4-isopropenylcyclohexanone (**3**), 14% *cis*- and 8% *trans*-2-methyl-3-isopropenylcyclopentanone (**4** and **5**), and 11% total of other products. The four major products were isolated by preparative glpc (XF-1150).

Octadienone **1** displayed ir (CCl_4) 5.94, 6.18, 10.1, and 10.4 μ; nmr δ 6.2 (m, 2, CH=CH_2), 5.7 (m, 1, C**H**=CH_2), 5.07 (m, 1, C=C**H**), 2.3 (m, 4), and 1.60 (broad s, 6); mass spectrum *m/e* (relative intensity) 138 (14), 83 (85), 70 (35), 69 (35), 68 (33), 67 (33), 55 (100), 41 (75), 27 (54).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.14; H, 10.18.

Cyclohexanone **3** showed ir 5.82, 6.07, and 11.2 μ; nmr δ 4.74 (m, 2, CH_3C=CH_2), 2.1 (m, 9), and 1.74 (t, 3, J = 1 Hz, CH_3C=CH_2); mass spectrum *m/e* 138 (34), 110 (20), 81 (43), 68 (100), 55 (54), 41 (48).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.86; H, 10.10.

trans-2-Methyl-3-isopropenylcyclopentanone (**5**) had ir (CCl_4) 5.75, 6.07, and 11.2 μ; nmr δ 4.80 (m, 2, CH_3C=CH_2), 2.1 (m, 6), 1.73 (t, 3, J = 1 Hz, CH_3C=CH_2), and 0.95 (d, 3, J = 6 Hz); mass spectrum *m/e* 138 (84), 123 (22), 96 (53), 82 (79), 81 (86), 67 (100), 55 (43), 41 (65).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.04; H, 10.14.

cis-2-Methyl-3-isopropenylcyclopentanone (**4**) was obtained in 85% purity as a mixture with **5**: ir 5.74, 6.06, and 11.2 μ; nmr δ 4.82 (m, 1, CH_3C=CH_2), 4.70 (m, 1, CH_3C=CH_2), 2.82 (broad quartet, 1, J = 7 Hz, C**H**CH_3), 2.1 (m, 5), 1.69 (m, 3, CH_3C=CH_2), and 0.82 (d, 3, J = 7 Hz, CHCH_3). Further purification could not be effected by glpc, apparently because of conversion of **4** to **5** on the glpc column.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.01; H, 10.08.

Pyrolysis of 1, 3, 4, and 5.—Approximately 15-mg samples of octadienone **1** (95%), cyclohexanone **3**, and cyclopentanones **4** (85% purity) and **5** were passed through the unpacked quartz tube at 570, 660, and 740°. The product mixtures were ex-

(14) J. M. Conia and P. Leriverend, *C. R. Acad. Sci., Paris*, **250**, 1078 (1960).

amined by glpc analysis. The significant data are summarized below. At 570° these four compounds were essentially the only constituents of the product mixtures. At 740° as much as 50% of the product mixtures consisted of unidentified materials. Pyrolysis of dienone **1** at 570° gave 70% conversion to a 3:2:1 mixture of **5**:**4**:**3**. At the same temperature, **3** gave only 10% conversion, mainly to **4** and **5**. Even at 740° less than half of **3** was rearranged (unidentified components taken into account), primarily to **4** and **5**. About 30% of the *cis*-cyclopentanone (**4**) was converted to the *trans*-cyclopentanone (**5**) at 570°. At the same temperature, about 15% conversion of **5** to **4** was obtained. These were essentially the only products at this temperature. At 740°, both **4** and **5** led to a mixture containing a 6:1 ratio of **5**:**4** as about 75% of the mixture. There were traces of dienone **1** and cyclohexanone **3** in these products.

Base-Catalyzed Interconversion of Cyclopentanones 4 and 5.—About 10 mg of sodium metal was dissolved in 5 ml of dry methanol and 20 mg of the *trans*-cyclopentanone was added. The solution was heated to reflux for 17 hr, diluted with water, and extracted with pentane. The product was shown by glpc to be 92% *trans*- and 8% *cis*-cyclopentanone. Similar treatment of an 85% pure sample of **4** led to a product mixture indicated to be 83% **5** and 17% **4**.

Irradiation of 7-Methylocta-1,6-dien-3-one (1).—A solution of 11 mg of **1** in 1.0 ml of purified hexane in a quartz test tube was degassed by bubbling prepurified nitrogen through the solution for 1 min with a pipet and sealed with a rubber serum cap. This solution was irradiated in a Rayonet reactor with a bank of sixteen 2537-Å bulbs for 1 hr. Glpc analysis indicated no change in the sample. Further irradiation with 3000-Å lamps for 4 hr caused formation of a white solid on the wall of the tube, but glpc assay failed to reveal any volatile products.

Another 10-mg sample of **1** in 5 ml of purified benzene in a 10-ml Pyrex flask was degassed as above. Acetone (2 drops) was added and the solution was irradiated at 3000 Å for 17 hr. Glpc examination again disclosed no volatile products.

Registry No.—**1**, 24903-94-4; **2**, 24903-95-5; **3**, 22460-53-3; **4**, 24903-97-7; **5**, 24903-98-8.

The Allylic Rearrangement of 3,3,3-Trichloro-1-propenyl Ketones

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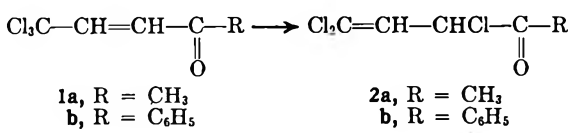
The anionotropic allylic rearrangement of 3,3,3-trichloro-1-propenyl methyl ketone (**1a**) and 3,3,3-trichloro-1-propenyl phenyl ketone (**1b**) has been investigated. It afforded 1,3,3-trichloro-2-propenyl methyl ketone (**2a**) and 1,3,3-trichloro-2-propenyl phenyl ketone (**2b**), respectively. The isomerization was catalyzed by various solids, *e.g.*, silica gel, alumina, acid clay, cobaltous oxide, cupric oxide, ferric oxide, and iron and copper powder but not by metal oxides of more ionic character, *e.g.* calcium oxide, magnesium oxide. The rearranged products primarily reacted with nucleophiles as α-chloro ketones. Diethylamine and triethylamine, however, catalyzed the prototropic rearrangement of **2a** and **2b** to give 1,3,3-trichloro-1-propenyl methyl ketone (**10a**) and 1,3,3-trichloro-1-propenyl phenyl ketone (**10b**). The intermediate diethylamine salt of **2b** (**12**) was isolated as a white powder and characterized. The transformation of **12** to **10b** was complete within a few days when kept at room temperature.

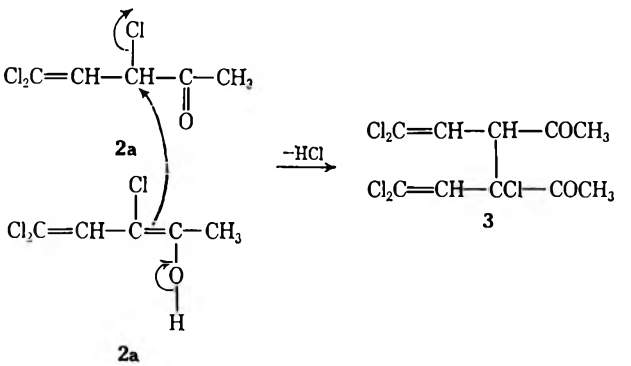
Allylic rearrangements of 1,1,1-trichloro-2-propenes have been reported by several authors. The isomerization of 1,1,1-trichloro-2-methyl-2-propene to 1,1,3-trichloro-2-methyl-1-propene has been studied by Kundiger, *et al.*[1] The reaction might be catalyzed by such materials as silica gel, thionyl chloride, antimony pentachloride, and alkaline soft glass powder, or proceed pyrolitically. Hexachloropropene-1-^{14}C was isomerized by heating at 120° for several hours and by the chromatographical treatment on silica gel.[2] We have recently found that 1-acyl-3,3,3-trichloro-1-propenes (**1**) also undergo the allylic rearrangement by the action of solid supports of glpc to form 1-acyl-1,3,3-trichloro-2-propenes (**2**). The α hydrogen in **2** is highly activated by the influence of adjacent groups so that they are subject to further chemical change.



1a, R = CH_3 **2a**, R = CH_3
b, R = C_6H_5 **b**, R = C_6H_5

This paper describes the catalytic transformation of 3,3,3-trichloro-1-propenyl methyl ketone (**1a**) and 3,3,3-trichloro-1-propenyl phenyl ketone (**1b**) to 1,3,3-trichloro-2-propenyl methyl ketone (**2a**) and 1,3,3-trichloro-2-propenyl phenyl ketone (**2b**) and discusses their structures and chemical properties.

The substrate **1a** was heated on a bath at 120–180° in the presence of solid materials as catalyst and distilled under a reduced pressure (20–30 mm) in order to investigate their effect on the present transformation. Strongly ionic substances such as calcium oxide, magnesium oxide, and sodium chloride did not catalyze the reaction. On the other hand, the presence of less ionic materials such as cobaltous oxide, cupric oxide, and ferric oxide catalyzed the reaction considerably with the partial formation of resinous products. Silica gel was most eminent in the catalytic action among solid supports used. A small amount of 3,4-bis(2′,2′-dichlorovinyl)-3-chloro-2,5-hexanedione (**3**) was usually produced as a by-product. A possible mechanism of the formation of **3** is tentatively given as shown in eq 1.



(1)

(1) (a) D. G. Kundiger and K. H. Groman, *J. Amer. Chem. Soc.*, **75**, 1744 (1953); (b) D. G. Kundiger and H. N. Haney, *ibid.*, **76**, 615 (1954).

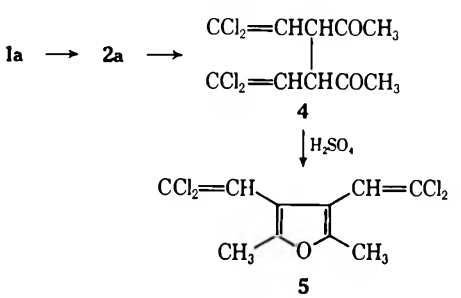
(2) C. H. Shuford, Jr., D. L. West, and H. W. Davis, *ibid.*, **76**, 5803 (1954).

The isomerization has occurred also in the presence of iron and copper powder. The transformation of **1b** with the presence of silica gel was conducted at higher temperatures (170–220°) successfully.

The structures of **2a** and **2b** were elucidated by ir and nmr data and elemental analyses. The ir absorption of **2a** at 1730 cm^{-1} is consistent for isolated C=O indicating that the conjugation of C=C and C=O has disappeared as a result of the rearrangement. In the ir spectrum of **1a** absorptions due to ν (C=O, cisoid) and ν (C=O, transoid) are observed at 1700 and 1676 cm^{-1}, respectively.[3]

The nmr spectrum of **2a** is decidedly different from that of **1a**. While **1a**, measured in deuteriochloroform, exhibits a singlet at τ 7.60 (3, methyl protons) and an AB quartet with centers at τ 2.94 and 3.43 (2, vinyl protons, J = 14 Hz), **2a** exhibits a singlet at τ 7.68 (3, methyl protons), a doublet at τ 3.96 (1, vinyl proton, J = 9 Hz), and a doublet at τ 5.08 (1, methine proton, J = 9 Hz). When **1a** was treated with copper powder at 120–180° white crystals melting at 71–73° were obtained in 23% yield along with the isomerized product (**2a**, 10%). Spectral data and elemental analyses indicate that this compound is 2,5-dimethyl-3,4-bis(2′,2′-dichlorovinyl)furan (**5**) as is evidenced by the fact that **2a** also gives **5** on the treatment with copper powder in the absence of solvent. It is therefore postulated that the cyclization to **5** proceeds *via* 3,4-bis(2′,2′-dichlorovinyl)-2,5-hexanedione (**4**) (Scheme I). Actually, when

SCHEME I



2a or **1a** was treated with copper powder in xylene, the intermediate (**4**) was produced in 35% yield. The cyclization of **4** to the furan (**5**) was realized also by the treatment with concentrated sulfuric acid. Uv absorption bands of **5** reveals the existence of the conjugated carbon–carbon double bond and furan ring [λ_{max} 219 mμ (ϵ 19,500) and 267 (18,000)]. The nmr spectrum of **5** is very simple, τ 3.56 (2, singlet) and τ 7.82 (6, singlet) in deuteriochloroform indicating its symmetrical structure as regards the ring. Furthermore, its furan ring resisted the hydrolysis with diluted sulfuric acid.[4] The increased stability of this compound might be attributable to the conjugation of two 2′,2′-dichlorovinyl groups with the furan ring. The present reaction may thus be an useful method for obtaining symmetrically substituted furan derivatives.

To investigate the reactivity of the rearranged product (**2a**) as an α-chloro ketone, it was allowed to react with several nucleophiles (Scheme II). It afforded

(3) R. D. Campbell and N. H. Cromwell, *J. Amer. Chem. Soc.*, **79**, 3456 (1957).

(4) The ring opening of furan derivatives is usually achieved by refluxing with 10% sulfuric acid (D. M. Young and C. H. F. Allen, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 220).

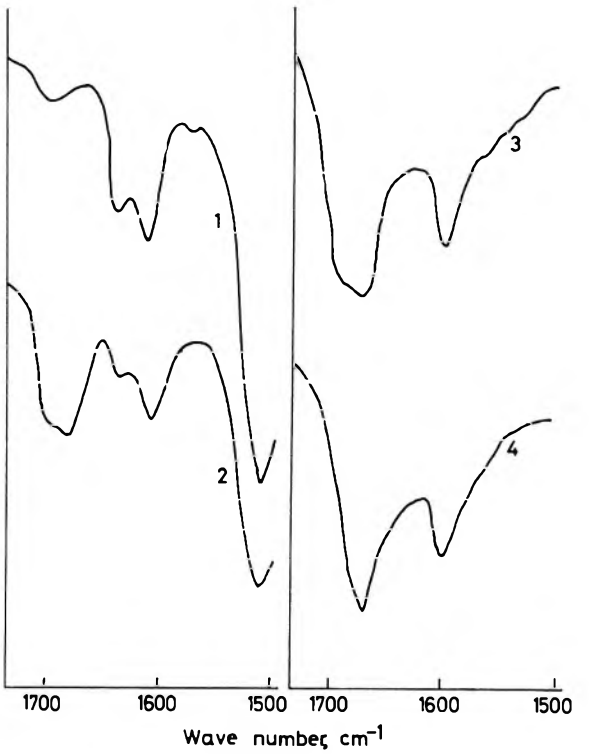
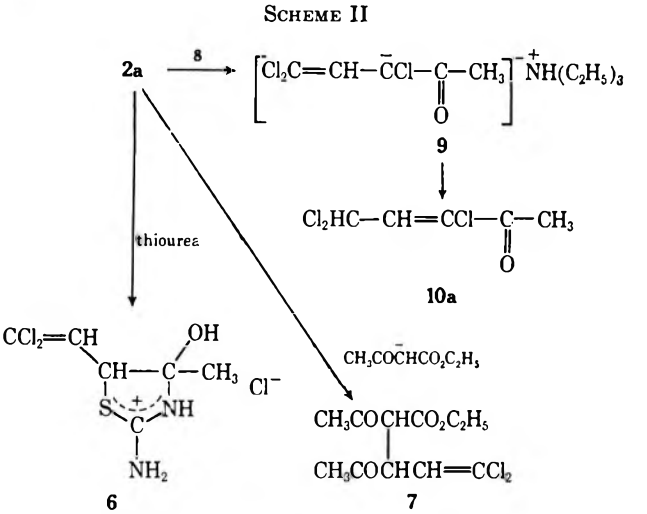


Figure 1.—The shifts in absorption bands of the amine salt (**12**) with time: (1) a few minutes after the formation, (2) 2 hr; (3) 2 days, (4) 2 weeks.

SCHEME II

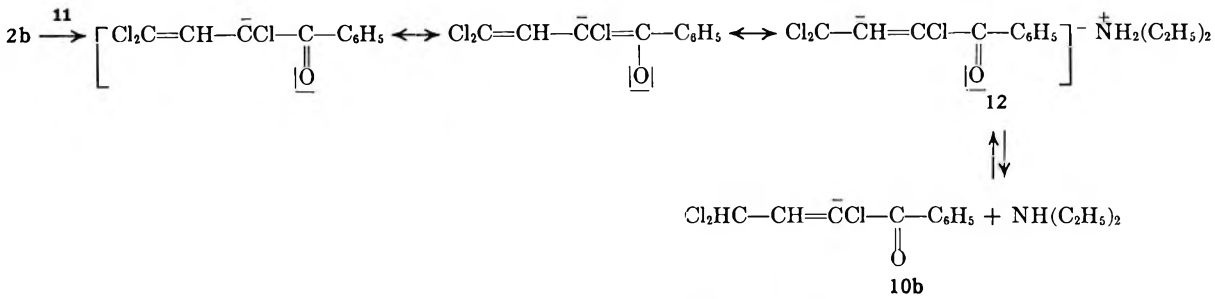


2-amino-4-methyl-4-hydroxy-5-(2′,2′-dichlorovinyl)thiazoline hydrochloride (**6**) with thiourea and 3-carbethoxy-4-(2′,2′-dichlorovinyl)-2,5-hexanedione (**7**) with ethyl sodioacetoacetate, whereas the reaction of **2a** with triethylamine (**8**) in ether solution resulted in the formation of 1,3,3-trichloro-1-propenyl methyl ketone (**10a**) in 62% yield.

It should be noted that in the ir spectra of **10a** the absorption due to ν (C=O) is observed only at 1700 cm^{-1} which is indicative of the cisoid structure. It is presumed that the repulsive force between chlorine and carbonyl oxygen of **10a** caused the disappearance of the transoid structure.

The mechanism of the transformation of **2** to **10** may be postulated as follows. The α-methine proton in **2** is acidic enough to transfer to and protonate **8**. The tertiary ammonium salt (**9**) produced intermediately is then transformed to **10** gradually. The above postula-

SCHEME III



tion has been evidenced by the fact that, in the reaction of 1,3,3-trichloro-2-propenyl phenyl ketone (**2b**) with diethylamine (**11**), the amine salt (**12**) was isolated as white crystals in 62% yield. Infrared absorption band of **12** originally observed at 1700 cm^{-1} (C=O, Nujol) has shifted to 1670 cm^{-1} in 1 day indicating that **12** has undergone the transformation to **10b** partly while being kept at room temperature (see Figure 1). The distillation of **12** also gave **10b** in 38% yield. The γ proton of **10b** is mobile since the diethyl amine salt (**12**) was reproduced on addition of **11** to **10b** (Scheme III).

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory. Analytical determinations by glpc were performed on Hitachi K-53 model gas chromatograph (3-mm o.d. × 1 m, 10% Apiezon Grease L on Chromosorb W), and preparative isolations by glpc were performed on Yanagimoto GCG-550T model gas chromatograph (3 mm o.d. × 2.25 m, 10% Apiezon Grease L on Chromosorb W). We are indebted to Dr. Akira Suzuki and Mr. Sigezo Simokawa, both of Hokkaido University, Sapporo, Japan, for nmr measurements. Microanalyses and spectral measurements of liquids were performed on samples collected by glpc.

Commercial grade materials were purchased and used as catalysts in the transformation without purification. 3,3,3-Trichloro-1-propenyl methyl ketone (**1a**) was prepared in 80% yield by the method of Salkind[5a] by treating chloralacetone[5b] with concentrated sulfuric acid: bp 95–100° (20 mm); mp 25–26° [lit.[5a] bp 93–94° (20 mm), mp 25–26°]; ir (liquid) 1700 (cisoid C=O), 1676 (transoid C=O), 1630 (C=C) and 737 cm^{-1} (C—Cl); nmr ($CDCl_3$) τ 2.94, 3.43 (q, 2, J = 14 Hz, –CH=CH—C=O), and 7.60 (s, 3). 3,3,3-Trichloro-1-propenyl phenyl ketone (**1b**) was prepared similar to the manners described in the literature:[5c] yield 81%; mp 98–99° (lit.[5c] mp 100°); ir (Nujol) 1652 (C=O), 1625 (C=C), 1595 (benzene C=C) and 740 cm^{-1} (C—Cl).

General Procedure for the Catalytic Transformation of 1a.—A mixture of equal amounts of **1a** and the catalyst was heated on a bath at 120–180° and distilled under diminished pressure (20–30 mm). The distribution of **1a** and **2a** in the distillate was determined by the measurement of infrared absorbances at 1730 cm^{-1} (C=O) for **2a** and at 737 cm^{-1} (C—Cl) for **1a**, respectively. The effects of solid materials on the transformation are as follows [substances, amounts of distillate (%), contents of **2a** (%) in distillate[6a]]: CuO, 16, 99; Fe, 16, 89; Cu, 33, 87; CoO, 33, 89; FeO, 23, 73; silica gel, 72, 58; alumina, 50, 73; acid clay, 93, 45; Celite 535, 93, 26; MgO, 90, 13; CaO, 93, 0; Na_2CO_3, 80, 0; FeS,[6b] 0, 0; PbO, 93, 5; NaCl, 86, 0; $SOCl_2$,[6c] 52, 73; HCl,[6d] 76, 34.

1,3,3-Trichloro-2-propenyl Methyl Ketone (2a).—A mixture of 50 g of **1a** and 50 g of silica gel on one treatment as above yielded 35.9 g of crude product of *ca.* 58% purity. Similar treatment repeated two times more afforded a product of at least 95% purity, yield 19.6 g (39%), bp 90–91° (19 mm). After distilling off a small amount of by-product (**3**, 1 g, see the next section) at 76° (15 mm), an analytical sample of the product was collected at 79–80° (12 mm) by fractional distillation using spinning-band column with the theoretical plate number of 70: $n^{27}D$ 1.4951.

Anal. Calcd for $C_5H_5Cl_3O$: C, 32.04; H, 2.69. Found: C, 31.88; H, 2.82.

3,4-Bis(2′,2′-dichlorovinyl)-3-chloro-2,5-hexanedione (3).—Analytical sample of the low-boiling fraction obtained in the above experiment was preparatively isolated by gas chromatograph: ir (liquid) 1721 and 1698 (C=O) and 1595 cm^{-1} (C=C).

Anal. Calcd for $C_{10}H_9Cl_5O_2$: C, 35.49; H, 2.68. Found: C, 35.48; H, 2.81.

1,3,3-Trichloro-2-propenyl Phenyl Ketone (2b).—From a mixture of 89 g (0.357 mol) of **1b** and 90 g of silica gel, 35.4 g (40%) of a liquid distilling at 145–146° (5 mm) was obtained by the same treatment as described in the foregoing experiment of **1a**: $n^{27}D$ 1.5752; ir (liquid) 1690 (C=O) and 1618 cm^{-1} (C=C).

Anal. Calcd for $C_9H_7Cl_3O$: C, 48.13; H, 2.83. Found: C, 48.41; H, 3.03.

3,4-Bis(2′,2′-dichlorovinyl)-2,5-hexanedione (4). (a) **From 3,3,3-Trichloro-1-propenyl Methyl Ketone (1a).**—Copper powder (6.6 g, 0.104 g-atom) was suspended in a solution of **1a** (10.0 g, 0.053 mol) in 30 ml of xylene. The mixture was heated under reflux on an oil bath for 1 hr. After filtration, removal of xylene, and recovery of **1a** (0.3 g, 3%) at 95–98° (20 mm), 3.0 g (37%) of a fraction distilling at 132–137° (20 mm) was collected: ir (liquid) 1725 (C=O) and 1620 cm^{-1} (C=C).

Anal. Calcd for $C_{10}H_{10}Cl_4O_2$: C, 39.51; H, 3.32. Found: C, 39.70; H, 3.30.

(b) **From 1,3,3-Trichloro-2-propenyl Methyl Ketone (2a).**—A solution of **2a** (2.1 g, 0.011 mol) in 6 ml of xylene suspended with copper powder (1.4 g, 0.022 g-atom) was refluxed for 1 hr. After filtration and removal of the solvent, a fraction distilling at 100–120° (5 mm) was collected, yield 0.8 g. Analysis by glpc indicated that this fraction consisted of roughly equal portions of **4** and **5**.

2,5-Dimethyl-3,4-bis(2′,2′-dichlorovinyl)furan (5).—In 10 ml of concentrated sulfuric acid, 1.2 g (0.004 mol) of **4** was dissolved. After being kept at room temperature for 5 min the solution was poured onto cracked ice. The organic layer was extracted with ether several times and the extracts were dried over Na_2SO_4. Removal of the solvent gave a deep yellow solid. Recrystallizations of the crude product from petroleum ether (bp 50–70°) yielded 0.5 g (44%) of white crystals: mp 71–73°; bp 120° (2 mm); ir (Nujol) 1603 (C=C) and 1584 cm^{-1} (furan C=C); uv max (98% C_2H_5OH) 219 (ϵ 19,500) and 267 (18,000); nmr ($CDCl_3$) τ 3.56 (s, 2), and 7.82 (s, 6).

Anal. Calcd for $C_{10}H_8Cl_4O$: C, 42.00; H, 2.82. Found: C, 41.95; H, 2.90.

Transformation of 1a to 5 by the Action of Copper.—A mixture of 19.7 g (0.105 mol) of **1a** and 20 g (0.315 g-atom) of copper powder was heated *in vacuo* at 90–110° at reflux. Heating was continued for 3 hr. The mixture was fractionally distilled to give 2.0 g (10%) of **2a** and a fraction which distilled at 120° (2 mm) and solidified immediately as white crystals, mp 71–73°. This proved to be **5** by ir spectroscopy, yield 3.5 g (23%). The ir spectrum of this product was superimposable with that of **5**.

Hydrolysis of 5.—A mixture consisting of acetic acid (10 ml), water (1 ml), 10% sulfuric acid (0.5 ml), and 0.5 g (0.0017 mol) of **5** was heated under reflux for 50 hr. On cooling 0.4 g of white crystals separated, mp 71–73° (from C_2H_5OH). No other product was detected in an appreciable amount. It did not show depression of mixture melting point with **5**.

(5) (a) I. Salkind, *J. Russ. Phys. Chem. Soc.*, **30**, 906 (1898); (b) H. Gault and G. Mennicken, *C. R. Acad. Sci., Paris*, **229**, 1239 (1949); (c) W. Koenigs, *Chem. Ber.*, **25**, 795 (1892).

(6) (a) The remainder was mainly **1a**. (b) Polymerization has occurred. (c) Ten grams of **1a** was refluxed for 20 hr with 30 ml of thionyl chloride under nitrogen gas. (d) With continuous stream of dry hydrogen chloride **1a** was heated at 100–110° for 15 hr.

2-Amino-4-methyl-4-hydroxy-5-(2',2'-dichlorovinyl)thiazoline Hydrochloride (6).—To a solution of 0.8 g (0.011 mol) of thiourea in 22 ml of ethanol was added 1.8 g (0.010 mol) of **2a** dropwise at 30–40°. The mixture was allowed to stand overnight. Removal of the solvent left a red-brown powder which on recrystallization from 80% ethanol gave 1.33 g (50%) of brown crystals. It showed one spot on tlc and became colorless after several recrystallizations from 80% C_2H_5OH: mp 192° dec: ir (Nujol) 3400 (OH), 2730 and 2600 (NH^+), 1650 (C=C), and 1610 cm^{-1} (NH_2).

Anal. Calcd for $C_6H_9Cl_3N_2OS$: C, 27.34; H, 3.44. Found: C, 27.49; H, 3.59.

3-Carbethoxy-4-(2',2'-dichlorovinyl)-2,5-hexanedione (7).—Sodium (0.9 g, 0.039 g-atom) was dissolved in 13 ml of absolute ethanol. Ethyl acetoacetate (4.9 g, 0.038 mol) was added to this solution. At reflux temperature, 7 g (0.037 mol) of **2a** was dropped into the mixture and refluxing was continued for 1 hr. The sodium chloride precipitate was removed by filtration. After evaporation of the solvent and recovery of **2a** (1.5 g, 21%), an oil distilling at 133–135° (2.5 mm) was obtained: yield 1.2 g (11%); $n^{25}D$ 1.4860; ir (liquid) 1730 (ester C=O), 1710 and 1684 (C=O), 1648 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_{14}Cl_2O_4$: C, 46.99; H, 5.02. Found: C, 46.87; H, 4.77.

1,3,3-Trichloro-1-propenyl Methyl Ketone (10a).—A solution of 2.2 g (0.022 mol) of triethylamine in 3 ml of anhydrous ether was added dropwise to a solution of 4 g (0.021 mol) of **2a** in 5 ml of anhydrous ether cooled in an ice bath. After standing overnight it was filtrated to remove a trace of a brown precipitate. It was washed several times with water and dried with Na_2SO_4. Distillation gave a fraction of oil boiling at 90–91° (15 mm): yield 2.5 g (63%) $n^{29}D$ 1.5049; ir (liquid) 1700 (C=O), and 1615 cm^{-1} (C=C); uv max (cyclohexane) 239 mμ (ε 9720), 322 (39); nmr ($CDCl_3$) τ 2.94 (d, 1), 3.44 (d, 1), and 7.51 (s, 3).

Anal. Calcd for $C_5H_5Cl_3O$: C, 32.04; H, 2.69. Found: C, 32.02; H, 2.90.

1,3,3-Trichloro-1-propenyl Phenyl Ketone (10b).—A solution of 3 g (0.012 mol) of **2b** in 5 ml of ether was added with ice cooling to 3.7 g (0.037 mol) of 8 dissolved in 10 ml of anhydrous ether. The reaction mixture was kept cold for 30 min and then washed thoroughly with water. Removal of the solvent left a yellow liquid which on distillation gave 1.5 g (50%) of a yellow oil, bp 128–131° (2 mm). Microanalyses and spectral measurements were performed on samples collected by column chromatography (silica gel, hexane): $n^{24}D$ 1.5768; ir (liquid) 1670 (C=O), 1618 (C=C), and 1595 cm^{-1} (benzene C=C).

Anal. Calcd for $C_{10}H_7Cl_3O$: C, 48.13; H, 2.83. Found: C, 47.91; H, 2.75.

Addition Product of Diethylamine with 2b (12).—To a solution of diethylamine (1.1 g, 0.015 mol) in 2 ml of anhydrous ether, **2b** (1.0 g, 0.004 mol) dissolved in 2 ml of ether was added dropwise with ice cooling. A brown precipitate was separated immediately. It was gathered by filtration and washed thoroughly with anhydrous ether on filter paper and air-dried, giving 0.8 g (62%) of the crude product: mp 50° dec; ir (Nujol) 2480 and 2350 (NH^+), 1700 (C=O, very weak), 1640 (C=C), and 1610 cm^{-1} (benzene C=C). Because of rapid decomposition this product could not be purified for analysis, and so its physical constants may be in doubt.

Shift of ir absorption bands in C=O region with time is graphed on Figure 1 in the text.

It is insoluble in water, acetone, tetrahydrofuran, and ether, but soluble in benzene and chloroform, and very soluble in ethanol.

Registry No.—**1a**, 1552-26-7; **1b**, 21100-66-3; **2a**, 24886-76-8; **2b**, 24886-77-9; **3**, 24886-78-0; **4**, 24886-79-1; **5**, 24886-80-4; **6**, 24886-81-5; **7**, 24886-82-6; **10a**, 24886-83-7; **10b**, 24886-84-8; **12**, 24886-85-9.

A Novel Reaction between Benzil and Certain Nucleophilic Agents in N,N-Dimethylformamide[1]

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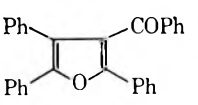
Benzil reacts with certain nucleophiles (phenoxide, *t*-butoxide, and hydroxide) in N,N-dimethylformamide to yield, in each case, benzoin benzoate (**3**) and the corresponding benzoylated nucleophile. *p*-Methoxybenzil reacts with sodium phenoxide to form *p*-methoxybenzoin anisate (**5**) and phenyl benzoate.

Perhaps the best known reaction of benzil with a nucleophile is that with hydroxide ion in which rearrangement occurs giving the conjugate base of benzilic acid.[2] Alkoxides are less successful in effecting the corresponding benzilic ester rearrangement except for those which have little or no tendency to transfer hydride ion. Thus, *t*-butoxide ion and methoxide ion react with benzil in alcoholic or benzene solution to yield the corresponding benzilic ester, whereas alkoxides containing more labile α hydrogens (*e.g.*, ethoxide and isopropoxide) lead to reduction products.[3] It is reported that the reaction between benzil and *t*-butoxide ion in diethyl ether results in the formation of benzilic acid.[4] Phenoxide ion fails to react with benzil in alcoholic or benzene solution, presumably owing to insufficient basicity on the part of the nucleophile.[4,5]

Phenoxide ion and benzil are likewise unreactive in dimethyl sulfoxide (DMSO) at room temperature. A reaction occurs at higher temperatures, although the products obtained do not incorporate phenoxide.[6,7] Phenoxide ion functions as a base to generate dimsyl ion, which then reacts with benzil to form 3-benzoyl-2,4,5-triphenylfuran (**1**), *cis*-α,β-dibenzoylstyrene (**2**), benzoic acid, and benzilic acid.



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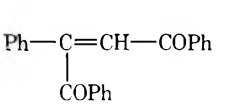

2

The present investigation was initiated to further confirm the necessity of DMSO to the formation of the products in the above reaction. In this respect the behavior of phenoxide ion toward benzil has been observed in a number of solvents. In the ethereal solvents, dimethoxyethane and diglyme, no reaction is en-

(1) Taken in part from the M.S. Thesis of J. D. Cheng.

(2) S. Selman and J. F. Eastham, *Quart. Rev.* (London), **14**, 221 (1960).

(3) W. von E. Doering and R. S. Urban, *J. Amer. Chem. Soc.*, **78**, 5938 (1956).

(4) G. A. Swan, *J. Chem. Soc.*, 1408 (1948).

(5) F. H. Westheimer, *J. Amer. Chem. Soc.*, **58**, 2209 (1936).

(6) J. C. Trisler, C. S. Aaron, J. L. Frye, and J. Y. Park, *J. Org. Chem.*, **33**, 1077 (1968).

(7) J. C. Trisler, J. K. Doty, and J. M. Robinson, *ibid.*, **34**, 3421 (1969).

countered even after extended periods at elevated temperatures. However, in N,N-dimethylformamide (DMF), a reaction occurs which results in the formation of benzoin benzoate (**3**) and phenyl benzoate (**4**) in near quantitative yields (eq 1).

$$2Bz_2 + PhO^- \longrightarrow \underset{\mathbf{3}}{Ph{-}CO{-}\underset{OBz}{\underset{|}{CH}}{-}Ph} + \underset{\mathbf{4}}{Ph{-}CO_2{-}Ph} \quad (1)$$

Unlike the reaction in DMSO where heating for extended periods is a necessary condition,[6] this reaction occurs very rapidly at or below room temperature. Stoichiometry was established by the fact that maximum yields ($\geq 90\%$) are obtained at a benzil–sodium phenoxide mol ratio of $\leq 2{:}1$ (yields based on benzil). Also, uv measurements have demonstrated that with the employment of a 4:1 mol ratio of benzil–sodium phenoxide, one-half the benzil remains after complete reaction.

The reaction of *p*-methoxybenzil with sodium phenoxide in DMF results in the formation of *p*-methoxybenzoin anisate (**5**) and phenyl benzoate (eq 2) although

$$p\text{-MeO}{-}Bz_2 + NaOPh \xrightarrow{DMF} \underset{\mathbf{5}}{p\text{-MeO}{-}PhCO{-}\underset{O_2CPh{-}OMe\text{-}p}{\underset{|}{CH}}{-}Ph} + Ph{-}CO_2Ph \quad (2)$$

the reaction appears slower and the yields are somewhat lower. The mechanistic significance of the directional influence by the *p*-methoxyl group is under investigation and will be the subject of a future report.

An explanation of these data invoking a solvent effect where the nucleophilicity of phenoxide ion is greatly enhanced in DMF[8] is untenable since similar results would then be predicted in DMSO where the reaction fails to occur.[6] Thus, it is indicated that the role of DMF is more subtle than a bulk medium effect. Argument for a specific solvent effect is strengthened by the observation that the reaction occurs with no decrease in yield in a DMSO solution containing 22% DMF.

Should benzil react directly with an "alkoxide" type reagent, the expected product is that resulting from a benzilic ester[3] (or acid[2]) rearrangement. However, instead of rearrangement (of the above-mentioned type), cleavage of the central C–C bond in one benzil molecule has occurred while the other benzil carbon skeleton remains intact. These considerations led us to investigate whether reactions between benzil and certain other nucleophiles are similarly influenced by DMF.

In this respect a reaction has been observed between benzil and sodium *t*-butoxide in DMF to form **3** and *t*-butyl benzoate (**6**) (eq 3). The yields have generally

$$2Bz_2 + t\text{-}BuO^- \underset{25°}{\xrightarrow{DMF}} \mathbf{3} + \underset{\mathbf{6}}{Ph{-}CO_2{-}t\text{-}Bu} \quad (3)$$

been around 50%. These results are of special interest since in other solvent systems different products are encountered; benzilic acid forms in ether[4] while *t*-butyl benzilate is the product in benzene or *t*-butyl alcohol.[3]

A genuine test of the "DMF effect" should be provided by the reaction between benzil and hydroxide ion.

(8) For a discussion of dipolar aprotic solvent effects on anionic reactions, see A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

That these reactants undergo the benzilic acid rearrangement under a variety of conditions is well documented.[2] The results of the reaction in DMF are given in Table I.

TABLE I

REACTION OF BENZIL WITH SODIUM HYDROXIDE IN DMF

Temp, °C	Yield of 3, %[a]	Yield of $PhCO_2H$, %[a]	Yield of Ph_2COHCO_2H, %[a]
−13	49	51	5
0	35	48	14
34	7	15	41

[a] Percentage yields are based on Bz_2 employed in a 2:1 mol ratio with sodium hydroxide.

That both the benzilic acid rearrangement and the reaction leading to **3** and benzoic acid have occurred is evident from a consideration of the data. Furthermore, it is apparent that a lowering of temperature causes a greater retardation in the rate of the rearrangement reaction. It is also observed that at the lowest reaction temperature, the quantities of **3** and benzoic acid are essentially the same, whereas at higher temperatures the ratio is decreased. This effect probably reflects the saponification of **3** at the higher temperatures. Indeed **3** is saponified with hydroxide in DMF at 0° to roughly the extent predicted from Table I.

The nature and extent of DMF involvement in this unique reaction of benzil and nucleophile is uncertain at the present time. However, it is interesting to speculate that the attack on benzil is nucleophilic in nature and that an alternate path to those "alkoxide"–benzil reactions previously established becomes possible in DMF. Furthermore, the influence of DMF must accommodate the attack of the weaker nucleophile, phenoxide ion, which is in general nonreactive toward the substrate in other solvent systems.

An extension of the present study to include other benzil–nucleophile reactions as well as an attempt to gain knowledge concerning the unique solvent effect is currently underway. This first report has defined a most unusual DMF alteration in the reaction path of certain benzil–nucleophile reactions. Also, for the first time a direct reaction between benzil and phenoxide ion has apparently been encountered.

Experimental Section[9]

Starting Materials.—Benzil was reagent grade material recrystallized from ethanol, mp 94–95°. *t*-Butyl alcohol was distilled from potassium metal. N,N-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from calcium hydride at reduced pressure (~20 mm). Other materials were either prepared by established procedures or were commercially obtained in general as reagent grade materials which were used without further purification.

Reaction of Benzil with Sodium Phenoxide in DMF.—Benzil (4.20 g, 20 mmol) was treated with sodium phenoxide[10] (1.16 g, 10 mmol) in 60 ml of DMF under a dry nitrogen atmosphere. After stirring at room temperature for 35 min, the mixture was poured into ice water, acidified, and extracted with ethyl ether. The ethereal solution was extracted with bicarbonate followed by aqueous sodium hydroxide (2.5%), washed with water, and dried over calcium chloride. The solution was then evaporated to a

(9) Melting points are uncorrected. The elemental analysis was carried out by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained using the Nujol mull technique. The nmr spectra were determined in $DCCl_3$ at 60 Mc using $Si(CH_3)_4$ as an internal standard.

(10) N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959).

20–30-ml volume after which a small quantity of petroleum ether (bp 30–60°) was added to induce crystallization. The cooled system was filtered to yield 2.70 g of benzoin benzoate (**3**), mp 123–124° (lit.[11] mp 124–125°). The filtrate was evaporated and the residue was triturated with petroleum ether to obtain crude phenyl benzoate (**4**) which was recrystallized from petroleum ether to afford 0.81 g of the purified material, mp 67.5–69° (lit.[12] mp 69°). Product identification was realized in each case from mixture melting point and infrared data.

The combined filtrates were evaporated, and the residue was dissolved in 10 ml of benzene and introduced onto a deactivated column of alumina (50 g of Alcoa F-20 alumina and 2 ml of 10% aqueous acetic acid). An additional 0.83 g of **4**, mp 67.5–69°, was eluted with petroleum ether (total yield of **4**, 83%). Unreacted benzil (0.20 g) was eluted with 95:5 petroleum ether–ethyl ether. Elution with 80:20 petroleum ether–ethyl ether yielded 0.14 g of additional **3**, mp 124–125° (from ether–petroleum ether). Total yield of **3** was 90%.

The bicarbonate wash from the initial ether extract was acidified and extracted with ether. The ethereal solution was washed with water, dried over calcium chloride, and evaporated to afford 0.18 g of acid residue. Sublimation resulted in 0.11 g of benzoic acid, mp 121–122°.

Very similar results were obtained where the reaction was conducted at −10° in DMF or at room temperature in a 22% DMF–DMSO solution.

Reaction of Benzil with Sodium *t*-Butoxide in DMF.—Sodium hydride[13] (1.17 g, 27 mmol) was treated with *t*-butyl alcohol (1.90 g, 25.7 mmol) in 70 ml of DMF. The system was stirred until the evolution of hydrogen gas had ceased. A solution of benzil (10.5 g, 50 mmol) in 30 ml of DMF was introduced under a dry nitrogen atmosphere. After stirring at room temperature for 1 hr, the contents were poured into ice water, acidified, and extracted with bicarbonate, washed with water, dried over calcium chloride, and evaporated to ~20 ml. Dilution with petroleum ether followed by cooling in an ice bath resulted in the crystallization of a white solid. Filtration and recrystallization from ethanol afforded 3.96 g of **3**, mp 123–124°. The ethanolic mother liquor was concentrated to yield 0.30 g of benzoin, mp 134–135°. Mixture melting point with an authentic sample in each case showed no depression.

The mother liquor from the initial filtration was evaporated and distilled to give 2.40 g (54% yield) of *t*-butyl benzoate (**6**), bp 81° (~4 mm) [lit.[14] bp 213° dec and 94° (10 mm)]. The infrared spectrum was identical with that of an authentic sample.

The residue (from distillation) was dissolved in 10 ml of benzene and placed on a deactivated column of alumina (100 g of Alcoa F-20 alumina and 4 ml of 10% aqueous HOAc). A red oil was obtained by elution with petroleum ether which yielded 2.10 g of benzil on trituration with ethanol. Further elution with 97:3 petroleum ether–ethyl ether afforded 0.16 g of additional **3**, mp 123–124° (total yield of **3**, 51%).

The bicarbonate solution was acidified and extracted with ether. The ethereal layer was washed with water, dried over calcium chloride, and evaporated. The residue was sublimed to yield 0.77 g of benzoic acid, mp 119–121° and 0.25 g of benzilic acid, mp 148–149° (from ether–hexane).

Reaction of Benzil with Sodium Hydroxide in DMF.—Benzil was treated with sodium hydroxide in DMF at room temperature, 0 and −13°. The results are summarized in Table I. A typical procedure is given below.

Sodium hydroxide was generated by the reaction of water (0.10 g, 5.5 mmol) and sodium hydride[13] (0.25 g, 5.8 mmol) in 55 ml of DMF. After the evolution of hydrogen gas had ceased, the system was cooled in an ice bath to −13°. A solution of benzil (2.10 g, 10 mmol) in 5 ml of DMF was added to the cooled suspension. The resulting system was stirred vigorously for 1 hr, poured into ice water, acidified, and extracted with ether. The ethereal solution was extracted with bicarbonate, washed with water, dried over calcium chloride, and evaporated to ~10 ml. Petroleum ether was added and heat was applied until dissolution was complete after which the solution was cooled in an ice bath. After crystallization was complete, filtration afforded 0.67 g of **3**, mp 123–124°. Mixture melting point with an authentic sample showed no depression.

The mother liquor was evaporated, the residue dissolved in 10 ml of benzene, and the resulting solution was placed on a deactivated column of alumina (50 g of Alcoa F-20 alumina and 1 ml of 10% aqueous acetic acid). Elution with petroleum ether resulted in the recovery of 0.74 g of benzil. Elution with 90:10 petroleum ether–ether afforded an additional 0.10 g of **3**, mp 123–124° (total yield of **3**, 49%).

The bicarbonate solution was acidified and extracted with ether. The ethereal solution was washed with water, dried over calcium chloride, and evaporated. Sublimation of the residue gave 0.31 g of benzoic acid, mp 121–122° (50.8% yield), and 0.11 g of benzilic acid, mp 148–149° (from ether–hexane).

Reaction of *p*-Methoxybenzil with Sodium Phenoxide in DMF.—Sodium phenoxide (0.30 g, 2.6 mmol) and *p*-methoxybenzil[15] (1.2 g, 5.0 mmol) were stirred in 30 ml of DMF at room temperature for 12 hr under a dry nitrogen atmosphere. The reaction mixture was worked up as previously described.

Sublimation of the acid portion afforded only a trace of *p*-methoxybenzoic (anisic) acid, mp 182–184° (ether–petroleum ether). Mixture melting point with an authentic sample showed no depression.

The neutral portion was obtained as an orange oil which was dissolved in 10 ml of benzene and introduced onto an alumina column (50 g of Alcoa F-20 alumina deactivated with 2 ml of 10% aqueous acetic acid). Elution with petroleum ether yielded 0.31 g (63% yield) of phenyl benzoate (**4**), mp 67–68° (from petroleum ether). Mixture melting point with an authentic sample showed no depression. Further elution with petroleum ether resulted in a trace of phenyl anisate, mp 72–73° (identified by mixture melting point). Elution with 87:13 solvent mixture afforded 0.15 g of *p*-methoxybenzil, mp 55–56°. Elution with ether produced a brown oil.

The oil was dissolved in a small quantity of ether, cooled in an ice bath, and diluted with petroleum ether. The container was scratched with a glass rod to induce crystallization. Filtration yielded 0.28 g (30% yield) of *p*-methoxybenzoin anisate (**5**), mp 91–92°. The infrared spectrum showed carbonyl absorption at 5.86 and 5.96 μ. The nmr spectrum showed two 3 H singlets (methoxyl) at δ 3.73 and 3.77, a 1 H singlet at δ 7.07 (methinyl), a 5 H multiplet at δ 7.2–7.7 (phenyl), and four 2 H doublets ($J \simeq 9.0$ cps) at δ 6.83, 6.97, 8.00, and 8.08 (two anisyl groups).

Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.43; H, 5.32. Found: C, 73.25; H, 5.39.

The mother liquor was evaporated; the residue was dissolved in 5 ml of benzene and rechromatographed. Only a brown oil, 0.37 g, was recovered. Attempts to resolve the oil were unsuccessful. However, the infrared spectrum was identical with that of **5**.

An authentic sample of *p*-methoxybenzoin anisate was prepared by acylating *p*-methoxybenzoin[15] with anisyl chloride under Schotten–Baumann conditions.[16] Mixture melting point with **5** showed no depression. Infrared and nmr spectra were identical for the two samples.

Registry No.—Benzil, 134-81-6; sodium phenoxide, 139-02-6; sodium *t*-butoxide, 865-48-5; sodium hydroxide, 1310-73-2; *p*-methoxybenzil, 22711-21-3; **5**, 24866-71-5.

Acknowledgment.—We are grateful to Messrs. C. S. Aaron and E. E. Green at Louisiana State University for obtaining the nmr spectra. Mr. Ben Stage helped in the preparation of some of the starting materials.

(11) N. Zinin, *Justus Liebigs Ann. Chem.*, **104**, 116 (1857).

(12) O. Dobner, *ibid.*, **210**, 246 (1881).

(13) Quantity of sodium hydride refers to a 56% by weight suspension in mineral oil. In each instance, mineral oil was removed by washing with petroleum ether.

(14) M. Pfannl, *Monatsh. Chem.*, **32**, 509 (1911).

(15) C. R. Kinney, *J. Amer. Chem. Soc.*, **51**, 1595 (1929).

(16) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 114.

Protonation of 2,4-Diaminopyrimidines. II. Dissociation Constants of 6-Amino Derivatives and Anion Effects in Moderately Strong Acid[1]

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Basic dissociation constants have been determined for the mono- and diprotonation of 2,4,6-triaminopyrimidine and several of its 5-substituted and 2-, 6-, and 4,6-N-substituted amino derivatives. The three overlapping dissociation constants for the 5-(*o*-aminophenylthio) analog were also obtained. Most of the dissociation constants for the second proton fall in the range of 10^{-2} to 10, and in a number of cases the slopes of the Hammett plots deviate significantly from 1. Furthermore, dissociation constants measured in sulfuric acid are appreciably different from those in hydrochloric acid, and Bunnett ϕ values are appreciably higher in the former solvent. It is postulated that ion-pair formation with large anions stabilizes the diprotonated species. The pK_1 and pK_2 values for the 5-substituted triamino derivatives are linearly related to the pK_1 values of the diamino analogs. However, the effect of N-substitution on pK_1 is quite different from that on pK_2 for the triamino compounds. Steric and solvation factors seem to be involved.

During a study of the acid-catalyzed cyclization of 2,4,6-triamino-5-(*o*-aminophenylthio)pyrimidines to 1,3-diazaphenothiazines,[3] it became important to know the pK_a values representing the association of the first, second, and third protons on the intermediate pyrimidines. This at first appeared to be a rather formidable problem, since the three pK_a values not only overlapped, but extended into the moderately strong acid region, where there was some doubt that the protonation followed the Hammett acidity function. Model pyrimidines, including 2,4,6-triaminopyrimidine and a number of 5-substituted and 2-, 6-, and 4,6-N-substituted derivatives, were therefore chosen for detailed studies of the first and second protonation.[4] The main purpose of this paper is to describe the properties of these compounds in mild to moderately strong acid (pH 2 to H_0 −3). An analysis of substituent effects upon the first and second dissociation constants is also presented.

Results

The pyrimidines studied, and their first and second dissociation constants and ultraviolet absorption spectra, are listed in Table I. The dissociation constants (K_1) for the symmetrical 2,4,6-triaminopyrimidines are corrected by a statistical factor of 2, since there is an equal probability of protonation on the equivalent ring atoms, N^1 and N^3, but only one possibility for proton loss. (Paper I of this series discusses the protonation at N^1, which is the most basic nitrogen of 2,4-diaminopyrimidine.)[1b] Similarly, the K_2 values for these compounds are corrected by a statistical factor of 0.5. All pK_a values were determined by spectrophotometric means.

The second protonation of these pyrimidines was found to occur in the moderately strong acid region. Measurements were made in sulfuric, hydrochloric, and perchloric acids in the case of **1**, and in sulfuric and hydrochloric acids with **3** and **9**. All other pK_2 values were measured in hydrochloric acid only.

The ultraviolet spectra of 2,4,6-triaminopyrimidine are depicted in Figure 1. Curves 5 and 6, for the diprotonated species in hydrochloric and sulfuric acids, respectively, show differing degrees of solvation shifts, which result in isosbestic loss in both the low and high wavelength region. Consequently, small vertical and lateral corrections for the isosbestic shift were made at the low wavelength minimum at 222 nm and small lateral corrections at the high wavelength maximum at 277 nm. Measurements were made at these two points only, to minimize the errors resulting from correcting or reading from a steep slope. All of the compounds presented this problem to varying degrees. Figure 2 presents one of the more difficult cases, with curve 5 showing a lateral isosbestic shift at 211 nm, a vertical shift at 254 nm, and only small species differences in the high wavelength region. The required correction was only 2.5% at 220 nm, however, since the difference in extinction coefficients between the mono- and diprotonated species at this wavelength is very large. This was the only region used for measurements with this particular compound.

Curves 3 and 4 of Figure 1, obtained at almost identical pH values in hydrochloric and sulfuric acids, respectively, illustrate that 2,4,6-triaminopyrimidine is protonated to a considerably greater extent in the latter acid at pH 1.1. Figure 2 (curves 2 and 3) shows similar phenomena with the 5-phenylthio analog. Measurements were made in increments of approximately 0.25 to 0.3 H_0 units for each pyrimidine, and least-squares plots computed for the Hammett acidity function (H_0)[5] *vs.* log I, where $I = [BH_2^{2+}]/[BH^+]$. This is illustrated for **1, 3, 5,** and **9** in Figure 3. The lines, although straight, are not parallel, and, in all three cases studied, those measured in sulfuric acid indicate a higher pK_a than in hydrochloric acid. The slopes of the lines are listed in Table I. In one experiment with **1** in hydrochloric acid, all solutions less than 0.4 M were made up to a constant chloride concentration of 0.4 M with sodium chloride. In this case, the pK_2 of **1** was raised to 1.41 ± 0.09. This value is

(1) (a) Presented in part at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, 1969. (b) Part I: B. Roth and J. Z. Strelitz, *J. Org. Chem.*, **34**, 821 (1969).

(2) After Sept 1, 1970, address correspondence to author at new company address: 3030 Cornwallis Road, Research Triangle Park, N. C. 27709.

(3) B. Roth, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., 1963; publication in preparation.

(4) The notation used here for pK_1 is for the equilibrium $B + H^+ \rightleftarrows BH^+$; pK_2 is used for $BH^+ + H^+ \rightleftarrows BH_2^{2+}$. Compound **4** gains three protons, and presumably the other bases can become triprotonated or even tetraprotonated in strong acid; hence the reversal of the usual convention.

(5) L. P. Hammett and A. J. Deyrup, *J. Amer. Chem. Soc.*, **54**, 2721 (1932).

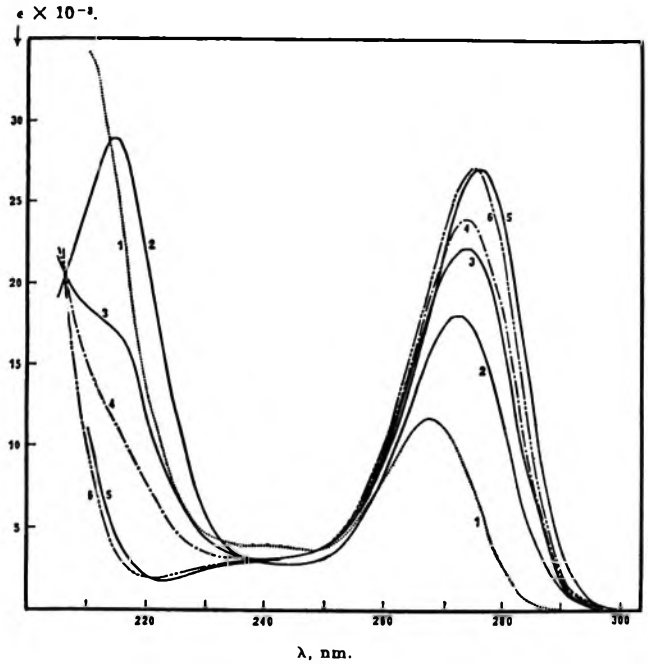


Figure 1.—Ultraviolet absorption spectra of 2,4,6-triaminopyrimidine: (1) as neutral species (pH 12), (2) as monocation (pH 4), (3) at pH 1.10 in hydrochloric acid, (4) at pH 1.09 in sulfuric acid, (5) as dication ($H_0 = -2$) in hydrochloric acid, (6) as dication ($H_0 = -2$) in sulfuric acid.

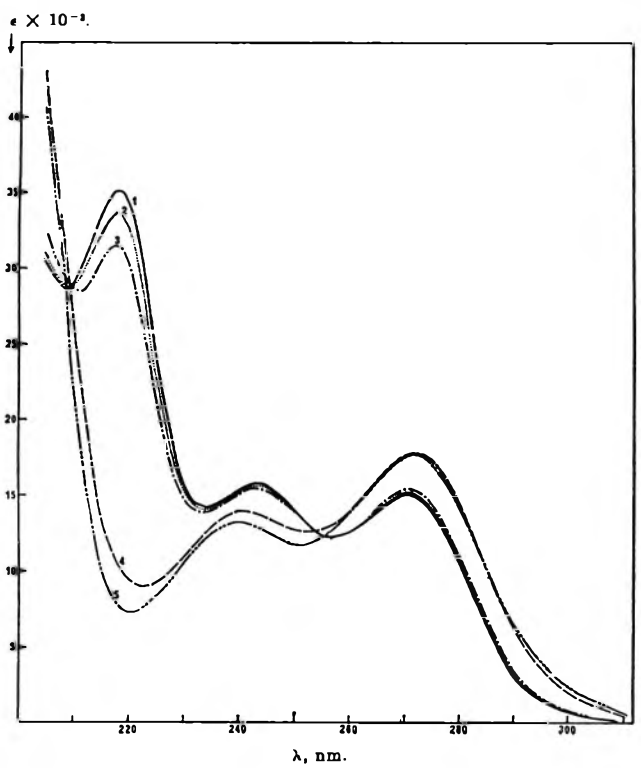


Figure 2.—Ultraviolet absorption spectra of 2,4,6-triamino-5-phenylthiopyrimidine: (1) as monocation (pH 3), (2) at pH 1.09 in hydrochloric acid, (3) at pH 1.09 in sulfuric acid, (4) at $H_0 = -1$ in sulfuric acid, (5) as dication ($H_0 = -3$) in sulfuric acid.

still considerably lower than that in sulfuric acid, despite the higher ionic strengths of the solutions.

The effect of monoanions of different size on the pK_2 of **1** was determined by swamping dilute hydrochloric acid solutions with sodium iodide, bromide, or chloride (10 × [HCl]), respectively. Results are shown in Table II. At pH 2.10, the differences are not significant, but the difference between iodide and bromide ion is significant at pH 1.55.

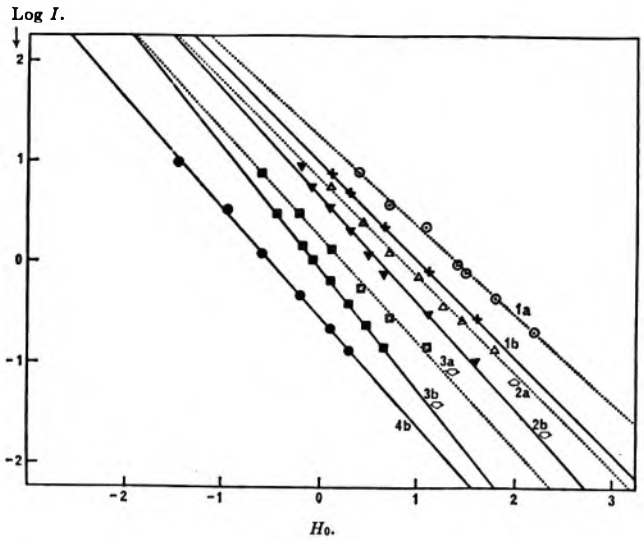


Figure 3.—Hammett plots of acidity *vs.* log ($[BH_2^{2+}]/[BH^+]$) for 2,4,6-triaminopyrimidine (1a and 1b); 2,4-diamino-6-piperidylpyrimidine (2a and 2b); 2,4,6-triamino-5-phenylthiopyrimidine (3a and 3b); 2,4,6-triamino-5-bromopyrimidine (4b). Dotted lines (1a–3a) represent sulfuric acid solutions; solid lines (1b–4b) represent hydrochloric acid.

TABLE II
EFFECT OF MONOANIONS ON DIPROTONATION OF 1

	% diprotonation	
Anion	pH 2.10	pH 1.55
I^-	12	36
Br^-	8	28
Cl^-	8	27

In the pH 7 region, divalent anions, such as HPO_4^{2-}, increase pK_1 to an extent greater than can be accounted for by the ionic strength. For example, the concentration pK_1 for **1** was found to be 6.97 in a phosphate buffer ($\mu = 0.16$), but was 6.78–6.81 in a phosphate buffer of $\mu = 0.016$, to which was added 0.36 *M* sodium chloride, sodium bromide, or sodium perchlorate. The phosphate buffer did not affect the isosbestic points in the manner described in paper I of this series.[2]

Figure 4 illustrates the ultraviolet absorption spectra of **4** as the neutral and tricationic species, as well as at three intermediate points. Since the three pK_a values overlap slightly, the separation of isosbestic points is incomplete. It was possible to calculate the pK_a values for each equilibrium at an isosbestic point for the next equilibrium, however, as indicated in Table I, footnotes *j*, *k*, and *m*, and illustrated by arrows in Figure 4. The second and third dissociation constants were also calculated at 217.5 nm (the low-wavelength maximum for curve 2, Figure 4), by use of the Thamer equation.[6] These results checked very closely with those obtained by the first method. Since these are macroconstants and do not represent protonation of a specific nitrogen, no statistical corrections were applied.

Discussion

The Pyrimidine Equilibrium $BH^+ \rightleftarrows BH_2^{2+}$.—Since the diprotonation of the triaminopyrimidines extends into the moderately strong acid region, where the acidity

(6) B. Roth and J. F. Bunnett, *J. Amer. Chem. Soc.*, **87**, 334 (1965).

TABLE

DISSOCIATION CONSTANTS AND ULTRAVIOLET ABSORPTION

Compd no.	Pyrimidine substituents 2	4	5	6	Acid for pK_2	Thermodynamic pK_2 (20°) from Bunnett plots[a,b]	pK_2 from midpoint of Hammett plots[b]	Slope, Hammett plot
1[c]	NH_2	NH_2		NH_2	HCl	1.31 ± 0.01[f]	1.31 ± 0.02[g]	−0.968 ± 0.023
					H_2SO_4	1.72 ± 0.03	1.69 ± 0.06	−0.881 ± 0.039
					$HClO_4$		1.46 ± 0.08	−1.08 ± 0.05
2[h]	NH_2	NH_2	C_2H_5	NH_2	HCl	1.55 ± 0.02	1.55 ± 0.04	−0.992 ± 0.041
3[i]	NH_2	NH_2	SC_6H_5	NH_2	HCl	0.08 ± 0.03	0.24 ± 0.01	−1.20 ± 0.019
					H_2SO_4	0.49 ± 0.08	0.52 ± 0.07	−1.05 ± 0.069
4[i]	NH_2	NH_2	$SC_6H_4NH_2(2)$	NH_2	HCl	−0.53 ± 0.04	−0.55 ± 0.04[j]	−0.983 ± 0.036
5[i]	NH_2	NH_2	Br	NH_2	HCl	−0.30 ± 0.08	−0.21 ± 0.03	−1.08 ± 0.036
6[i]	NH_2	NH_2	Cl	NH_2	HCl	−0.35 ± 0.02	−0.26 ± 0.02	−1.09 ± 0.014
7[n]	NH_2	NH_2		$NHCH_3$	HCl	1.05 ± 0.04	1.04 ± 0.05	−0.986 ± 0.041
8[n]	NH_2	NH_2		$N(CH_3)_2$	HCl	0.68 ± 0.03	0.69 ± 0.02	−1.06 ± 0.003
9[n]	NH_2	NH_2		$N(CH_2)_5$	HCl	0.58 ± 0.04	0.61 ± 0.05	−1.06 ± 0.051
					H_2SO_4	0.85 ± 0.03	0.84 ± 0.05	−0.967 ± 0.041
10[i]	NH_2	NH_2		$N(CH_2CH_2)_2O$	HCl	−0.35 ± 0.02	−0.14 ± 0.003	−1.25 ± 0.007
11[i]	NH_2	$N(CH_3)_2$		$N(CH_3)_2$	HCl	0.80 ± 0.05	0.82 ± 0.10	−1.22 ± 0.077
12[i]	NH_2	$N(CH_2)_4$		$N(CH_2)_4$	HCl	1.67 ± 0.07	1.67 ± 0.06	−1.09 ± 0.052
13[i]	$N(CH_2)_5$	NH_2		NH_2	HCl	0.86 ± 0.03	0.86 ± 0.03	−1.01 ± 0.041
14[k]	NH_2	NH_2	$CH_2C_6H_5$	NH_2				
15[o]	NH_2	NH_2	$C_6H_4Cl(4)$	NH_2				
16[p]	NH_2	NH_2	NHCHO	NH_2				
17[q]	NH_2	NH_2	$N{=}NC_6H_5$	NH_2				
18[q]	NH_2	NH_2	$N{=}NC_6H_4Cl(4)$	NH_2				
19[r]	NH_2	NH_2	NO_2	NH_2				

[a] J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, 44, 1899 (1966). [b] pK_2 taken as midpoint of Hammett plots, where $\log I = 0$. Rigorously, this is the thermodynamic pK_a value only when the slope is unity. In cases of marked deviation, such as 3a and 10, the Bunnett plots give the more accurate constant, in the absence of a new acidity function. Midpoints were calculated from the plot of $\log I = AH_0 + C$, where $I = [BH_2^{2+}]/[BH^+]$, A is the slope, C is the intercept at $H_0 = 0$, and $pK_2 = -C/A$. Data for the points were chosen between $\log I = \pm 1$. The number of points (n) and acid concentrations which are listed are the number of points and acid concentrations falling in this range. Statistical corrections of 0.5 are applied to K values for symmetrical derivatives. [c] Statistical corrections of 2 are applied to K values for the symmetrical pyrimidines. The limits recorded are the total range of values from calculations at *ca.* 10 wavelengths. [d] Observed endpoints in HCl solutions. Small medium shifts occurred in λ_{max}. [e] Reference 2. [f] Standard deviations. [g] Calculated from standard deviations of A/B in Hammett plots. [h] P. B. Russell and G. H. Hitchings, *J. Amer. Chem.*

I

SPECTRA OF 2,4,6-TRIAMINOPYRIMIDINE DERIVATIVES

				Ultraviolet absorption spectra					
				Neutral species		Monocation		Dication[d]	
ϕ[a]	n	Acid concn range, M	Thermodynamic[c] pK_1 (20°)	λ_{max}	$\epsilon \times 10^{-3}$	λ_{max}	$\epsilon \times 10^{-3}$	λ_{max}	$\epsilon \times 10^{-3}$
0.24 ± 0.13	6	0.026–0.6	6.72 ± 0.01[f]	209	35.2	214	29.2	277	26.7
0.83 ± 0.32	7	0.006–0.25		237.5 sh	4.01	272	18.2		
	4	0.01–0.3		267.5	11.80				
0.22 ± 0.29	4	0.01–0.41	6.84 ± 0.02	237.5 sh	5.51	215.5	23.5	245	4.60
				274.5	11.6	240 sh	4.60	285	25.0
						280.5	17.2		
−0.91 ± 0.14	7	0.2–1.5	5.66 ± 0.06	247.5	17.0	218	35.6	241	13.2
−0.16 ± 0.34	6	0.1–1.6		265	14.9	243	16.3	273	18.5
						271	15.5		
0.65 ± 0.08	7	0.4–4.2	2.59 ± 0.05[k]	214.5	58.0	215	48.4	248[l]	14.2
			5.95 ± 0.05[m]	247.5	15.1	245.1	14.3	273	19.4
				260–265 sh	12.9	271	14.2		
−0.18 ± 0.19	6	0.4–4.2	5.17 ± 0.02	234 sh	6.75	216	23.9	252	5.30
				274.5	9.05	245 sh	4.39	289	20.0
						282	14.5		
−0.27 ± 0.05	5	0.4–2.9	5.15 ± 0.02	235 sh	5.30	215	23.4	247.5	4.35
				274	9.40	242.5 sh	4.20	288	21.0
						282	14.5		
−0.04 ± 0.40	6	0.03–0.60	7.21 ± 0.03	213	35.8	217.5	26.0	280	29.0
				270	13.3	274	20.2		
−0.29 ± 0.26	6	0.03–0.79	7.21 ± 0.03	217.5	29.4	223	20.0	285	29.0
				275	14.6	279	21.9		
−0.47 ± 0.28	8	0.026–1.0	7.20 ± 0.03	220	27.8	229	20.1	290	31.4
0.18 ± 0.11	7	0.01–0.5		277	16.5	282	24.4		
−1.06 ± 0.14	5	0.2–1.5	6.73 ± 0.04	219	29.4	231	22.3	291	32.9
				275.5	16.5	281	24.8		
−0.99 ± 0.44	7	0.1–1.0	7.18 ± 0.02	228	36.5	230	23.4	297	30.8
				279	16.9	286	24.9		
−0.55 ± 1.1	4	0.01–0.3	7.56 ± 0.02	230.2	37.5	232.5	26.7	297.5	39.2
				281	22.0	288.2	31.8		
−0.019 ± 0.13	5	0.1–1.0	6.78 ± 0.03	247.5	11.9	227.5	30.8	247.5	7.35
				275	9.00	247.5 sh	7.40	280	24.2
						280.5	15.0		
			6.55 ± 0.02	237.5 sh	8.12	242.5 sh	6.42		
				273	11.4	278.5	16.8		
			6.19 ± 0.04	271	14.4	215.5	33.1		
						276	18.4		
			5.73 ± 0.03	233.5 sh	6.71	215	28.8		
				267	10.8	272	16.3		
			4.97 ± 0.04	248	14.9	215	22.0		
				255 sh	14.3	232.5 sh	14.9		
				375	23.8	257.5	9.65		
				397.5 sh	17.5	285 sh	5.95		
						364	22.5		
						395 sh	12.3		
			4.91 ± 0.05	252	18.5	215	24.1		
				257.5 sh	16.9	235 sh	17.1		
				381	28.7	257.5 sh	11.1		
				405 sh	22.7	282.5 sh	4.21		
						369.5	27.8		
						397.5 sh	17.9		
			3.22 ± 0.04	230 sh	17.7	214	44.0		
				335	36.0	235 sh	31.3		
						322	27.6		

Soc., 74, 3443 (1952). [i] Reference 3. [j] pK_3. pK_a values overlapped slightly; calculation was made from data at 232.5 and 276 nm, crossover points for the next equilibrium. No statistical corrections were applied to dissociation constants for this compound. [k] pK_2. Calculation from data at 265 and 295 nm, which are isosbestic points for the equilibrium $BH^+ \rightleftarrows B$, and also a region of very small change for the equilibrium $BH_3^{3+} \rightleftarrows BH_2^{2+}$. [l] Trication. [m] p$K_1$. Calculation from data at 276 nm, which is an isosbestic point for the next equilibrium. [n] B. Roth, J. M. Smith, and M. Hultquist, *J. Amer. Chem. Soc.*, 72, 1914 (1950). [o] Prepared by Paul Stenbuck in these laboratories, mp 280–282°; see also British Patent 712,595 (1954). [p] W. Traube, *Ber.*, 37, 4544 (1904). [q] These compounds were kindly donated by Drs. A. M. Triggle and D. J. Triggle of the State University of New York at Buffalo, Buffalo, N. Y. See J. Hampshire, P. Hebborn, A. M. Triggle, D. J. Triggle, and S. Vickers, *J. Med. Chem.*, 8, 745 (1965). [r] S. Gabriel, *Ber.*, 34, 3362 (1901).

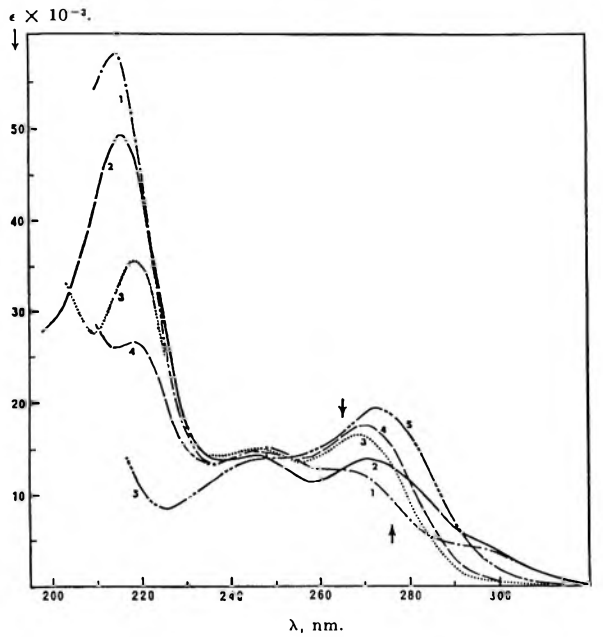


Figure 4.—Ultraviolet absorption spectra of 2,4,6-triamino-5-(*o*-aminophenylthio)pyrimidine: (1) as neutral species (pH 12), (2) at pH 4.02 (0.01 *N* acetate), (3) at pH 1.09 (in hydrochloric acid), (4) at $H_0 = -0.20$ (1 *N* hydrochloric acid), (5) at $H_0 = -3$ (hydrochloric acid).

of the solutions cannot be measured with the hydrogen electrode, the use of an acidity function approach is indicated for the measurement of pK_2. The Hammett acidity function, H_0,[5] which is defined as

$$H_0 = -\log a_{H^+} f_B/f_{BH^+} = pK_{BH^+} - \log [BH^+]/[B] \quad (1)$$

is the measure of the capability of a solution to transfer a proton to a *neutral* base B, to form its conjugate acid, BH^+. Hammett envisaged a second acidity function, H_+, for monocation–dication equilibria.[7] This function has not received extensive study, but, over certain ranges of sulfuric acid concentration, a parallelism with H_0 has been found.[8,9] Failure of certain bases to adhere exactly to the H_0 scale was found to be unrelated to a particular charge type.[10] It therefore seemed reasonable to compare log I with H_0 in our case. By definition (eq 1), the slope of such a plot should be 1. The results of Table I indicate that this is usually, but not invariably, the case with the pyrimidines tested. Figure 3 illustrates this point. Although no deviations are large, they are significant in a few cases, and the resultant pK_2 values calculated from eq 1 are inaccurate.

Bunnett and Olsen[11] have devised a method for the calculation of the thermodynamic pK_a for any base, regardless of the acidity function it follows. Use of the single acidity function H_0 in the equation

$$\log ([SH^+]/[S]) + H_0 = \phi(H_0 + \log [H^+]) + pK_{SH^+} \quad (2)$$

gives linear plots from which the desired pK_{SH^+} values can be obtained. Results by this method were found to agree well with the literature data obtained by the acidity function method, using a wide variety of substrates (S) which are not Hammett bases.[11] The slope of the plots, ϕ, is a parameter which expresses the response of the equilibrium to changing acid concentration, and may be interpreted in terms of hydration changes. The more positive the ϕ value, the greater is the hydration of SH^+ relative to S, according to the hydration hypothesis.

A comparison of the pK_2 values of Table I, calculated by the Bunnett *vs.* the Hammett method, shows them to be the same, within experimental error, except for the few cases where the slope definitely deviates from 1. The Bunnett equation values are considered to be the thermodynamic constants for the pyrimidines.

By definition, a thermodynamic pK_a value is a constant, which is not dependent on the medium. This presents an anomaly when we are faced with the data on **1**, **3**, and **9**, which show the thermodynamic pK_2 values to be higher by 0.2 to 0.4 pH units in sulfuric than in hydrochloric acid, and to be intermediate in the one case with perchloric acid. This phenomenon is not restricted to the moderately strong acid region, where the activity of water is less than 1. Much of the data was collected in solutions above pH 1, where the pH values can be determined by direct measurement. This is illustrated in Figure 1. Solutions **3** and **4** had almost identical pH values; it is clear that they differ considerably in their degree of protonation, however. This was also true of solutions at pH 1.5–1.6 with and without added salts. It could be argued that the sulfuric and hydrochloric end points (curves 5 and 6) are slightly different, and that the medium corrections may have been erroneous, which will change the pK_a values slightly. This is quite beside the main point, however. The difference in **3** and **4** suggests that the two substrates are actually different from each other, which can best be explained by different degrees of ion pairing of the diprotonated pyrimidine with chloride and bisulfate anions. Stronger ion pairing with the larger bisulfate ion (and with sulfate dianion present to a small extent) would contribute to greater stabilization of the diprotonated species. Evidence for this was also supplied by the fact that slight isosbestic shifts occurred in sulfuric acid in the pH 1.5–2.5 region if the ionic strength was not kept constant. Evidence for stabilization of the monoprotonated species by HPO_4^{2-}–$H_2PO_4^-$ anions at pH 7 was also indicated by an increase in pK_1 greater than could be accounted for by increased ionic strength.

Previous evidence for ion pairing in aqueous solution was obtained with diaminopyrimidines in phosphate buffers at pH 7.[2] Evidence for increased ion pairing as a function of monoanion size was obtained from the nmr spectra of 2,4-diaminopyrimidine hydrochloride, bromide, and iodide salts in dimethyl sulfoxide solution.[12] In the present series, iodide ion contributed more to stabilization of the dication than did bromide or chloride. Paul and Long have described similar salt effects with *p*-nitroaniline and other bases, as a function of anion size.[13]

Most of the ϕ values presented in Table I have a high standard error. This is to be expected at the low acidity of most of these experiments, since the expres-

(7) L. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter IX.
(8) T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 264 (1957).
(9) L. Michaelis and S. Granick, *J. Amer. Chem. Soc.*, **64**, 1861 (1942).
(10) R. L. Reeves, *ibid.*, **88**, 2240 (1966).
(11) See Table I, footnote *a*.
(12) B. Roth, S. Hurlbert, J. Strelitz, and G. H. Hitchings, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., 1966, to be published.
(13) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957), and references therein.

sion (H_0 + log [H$^+$]) of eq 2 approaches, and is sometimes equal to, zero. Since the margin of error in known H_0 values is relatively large,[13] it is evident that such errors will cause a large scatter in the points in this situation. In spite of this difficulty, the differences in the ϕ values of Table I are sufficiently great to make it possible to draw some reasonable conclusions about them.

The ϕ values for the equilibria in hydrochloric acid all fall in the range of +0.2 to −1.1. In general, the values become more negative with increasing alkylation of amino groups, or with the introduction of bulky 5 substituents. This would be expected on the basis of the hydration hypothesis. Since the ϕ values are not all substantially equal, it follows that this set of bases does not follow a common acidity function, as was also concluded on the basis of the Hammett plots. The ϕ values in sulfuric acid are all about 0.6–0.7 units higher than those in hydrochloric acid. By the hydration hypothesis, this would imply relatively greater hydration of the diprotonated species in sulfuric acid. We have already concluded that greater solvation occurs in the form of ion pairing with bisulfate ion. These hypotheses are probably not mutually exclusive.

The Effect of 5 Substituents on pK_1.—Figure 5 is a plot comparing the pK_1 values of the 2,4,6-triamino-5-substituted pyrimidines with those of their 2,4-diamino-5-substituted counterparts.[2] A good linear relationship is observed. A least-squares computation for the 8 substituents shown by solid circles on the graph gives the relationship

$$pK_{Tri} = 1.30 + 0.720pK_{Di} \quad (3)$$

The 95% confidence limits for the slope and intercept are, respectively, ±0.062 and ±0.367; s = 0.105 and r = 0.996. Since the diaminopyrimidines (paper I) obey the relationship

$$pK_{Di} = 7.32 - 6.96(0.738\sigma_I + 0.262\sigma_R^-) \quad (4)$$

the triaminopyrimidine constants can be calculated directly if σ is known. Stated in words, the polar effect of 5 substituents is less for the triaminopyrimidines by a factor of 0.72.

Relative Effects of Substituents on pK_1 and pK_2.—Table III shows ΔpK_a values for several groups of triaminopyrimidine derivatives. In series A, a comparison of ΔpK_1 and ΔpK_2 for the 5-substituted derivatives shows the differences to be very nearly equal for the four compounds studied. In other words, the substituent effect in the moderately strong acid region is very nearly the same as it is at neutrality. This is not true of the N-substituted derivatives, however, regardless of whether or not they are symmetrical.

Series B, the 6-(substituted amino)pyrimidines, shows the 6-methylamino, dimethylamino, and piperidino derivatives to be stronger bases than 1 by about 0.5 pH units in the pK_1 region. Such pyrimidines can be expected to protonate at N^3 rather than N^1, on both steric and electronic grounds. In contrast, other 2,4-diamino-6-substituted pyrimidines protonate at N^1.[1b] An indication that the protonation site is actually different is obtained from Figure 5 of paper I,[1b] which shows a very close correlation of 6-substituted pyrimidine pK_a values with a σ constant which is almost purely inductive. The data for the 6-dimethylamino derivative (σ = 0.065, pK_1 = 7.21) would give a point which falls way above the line. In other words, it is a stronger base than is expected from N^1 protonation. Since this substituent has a greater electron-donating capacity than does NH$_2$, protonation to give IIa and the *p*-quinonoid canonical form IIb is indicated. The protonation site for the less basic 6-morpholinopyrimidine is less certain. On steric grounds, N^3 is favored. See Scheme I.

In the pK_2 region, the 2,4-diamino-6-(substituted amino)pyrimidines are all *weaker* bases than the parent compound, and a progressive base weakening occurs in going from mono- to dialkylation. The large changes in ultraviolet spectra on diprotonation (see Table I and Figures 1 and 2) indicate that the second proton also goes on a ring nitrogen (N^1), to give IIIa. Of the possible canonical forms, IIIb–e, those most likely would

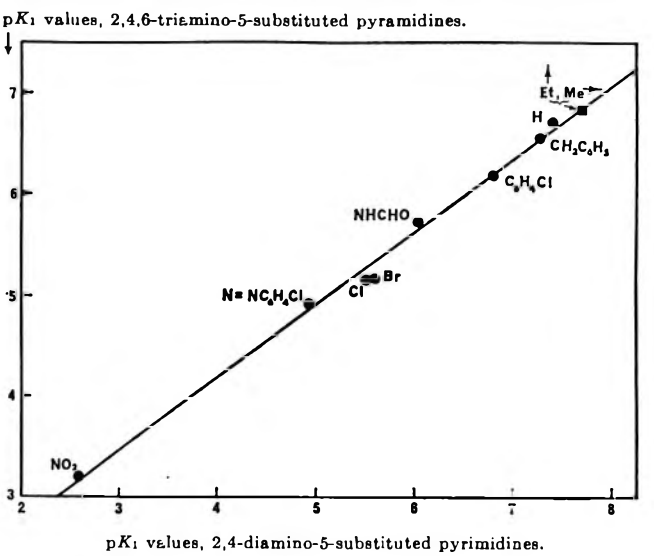


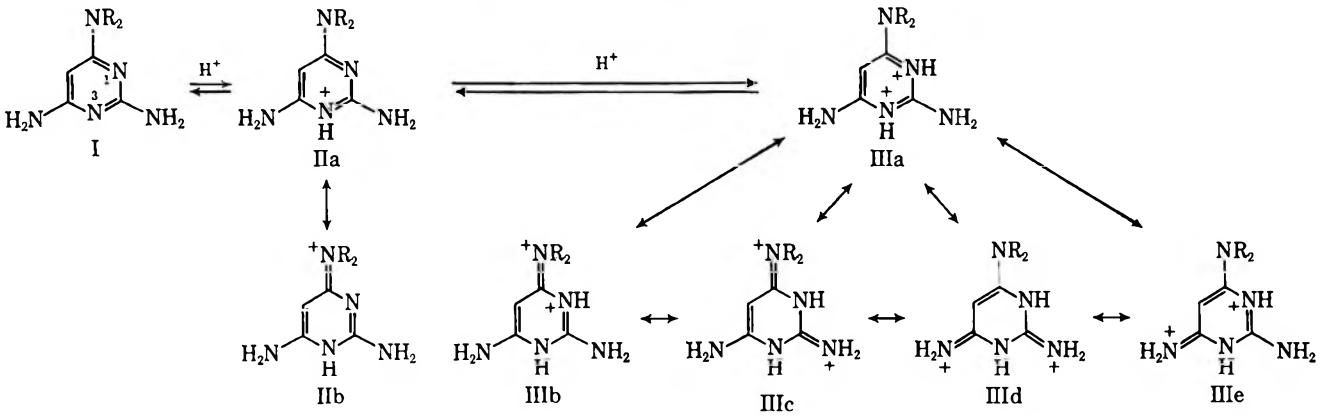
Figure 5.—Comparison of 5-substituent effects on the dissociation constants of 2,4,6-triamino- *vs.* 2,4-diaminopyrimidines.

TABLE III

COMPARISON OF ΔpK_1 AND ΔpK_2 VALUES FOR 2,4,6-TRIAMINOPYRIMIDINE DERIVATIVES

Substituent	ΔpK_1	ΔpK_2
A. pK_a (2,4,6-Triamino-5-substituted Pyrimidine) − pK_a (Compound 1)		
C_2H_5	0.12	0.24
SC_6H_5	−1.06	−1.23
Br	−1.55	−1.61
Cl	−1.57	−1.66
B. pK_a [2,4-Diamino-6-(substituted amino)pyrimidine] − pK_a (Compound 1)		
$NHCH_3$	0.49	−0.26
$N(CH_3)_2$	0.49	−0.63
$N(CH_2)_5$	0.48	−0.73
$N(CH_2CH_2)_2O$	0.01	−1.66
C. pK_a [2-Amino-4,6-bis(substituted amino)pyrimidine] − pK_a (Compound 1)		
$N(CH_3)_2$	0.46	−0.51
$N(CH_2)_4$	0.84	0.36
D. pK_a [2-(Substituted amino)-4,6-diaminopyrimidine] − pK_a (Compound 1)		
$N(CH_2)_5$	0.06	−0.45

SCHEME I



have their charges widely separated. Since N^1 is *ortho* to the 6-substituted amino group, the data suggest steric hindrance to diprotonation with increasing bulk. In the pyridine series, *ortho* substitution by isopropyl and *t*-butyl groups resulted in steric hindrance to protonation, but an ethyl group did not.[14] In contrast to ethyl, a methylamino group can be solvated, however. A comparison of the four ΔpK_2 values with the ϕ parameters is of interest. The latter are, in sequence, −0.04, −0.20, −0.47, and −1.06. This is suggestive of a linear correlation, and, in fact, a least-squares computation gives a correlation coefficient of 0.994 (t = 3.9, s = 0.059, and the slope is −0.72 ± 0.11). These results are no doubt fortuitous, but it is reasonable to assume that the decreasing ease of protonation is at least partially related to differences in solvation as hydrophobic groups are introduced. Considerably more data would be required to separate the various factors involved.

The C series, consisting of the 4,6-bis(dimethylamino) and pyrrolidino derivatives, shows a rather dramatic difference in the two compounds. The latter is not only a considerably stronger base in the pK_1 region, but remains a stronger base than **1** at pK_2. The C–N bond angles here are such as to greatly decrease the steric effect. The ϕ value is also less negative by 0.44 unit in the latter case.

The 2-piperidinopyrimidine (series D) has a pK_1 value very close to that of **1**, and thus it is a weaker base than the 6-piperidino analog. This is not unexpected, since there appears to be only a very small *ortho* resonance-stabilizing effect from the 2 position. In the pK_2 region, however, it is a stronger base than the 6 isomer. Since the steric effect at N^1 would appear to be the same from the 2 and 6 positions, another explanation would seem necessary. The pK_a values for this compound were corrected for the symmetry of the pyrimidine, and it is very possible that the molecule is actually not symmetrical in a medium where it is strongly solvated, if the 2-piperidino group is restricted in its rotation. In this case, pK_2 for **13** is 0.56, and ΔpK_2 is 0.75; these values are almost the same as those for **9**. The 2-piperidinopyrimidine has a less negative ϕ value, however; so the question remains unresolved.

(14) H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, **77**, 1723 (1955).

Experimental Section

pK_a Determinations.—The pK_1 values were determined according to procedures described in paper I of this series.[2] In the pK_2 range, the H_0 values used for solutions in sulfuric and hydrochloric acids were those of Paul and Long.[13] The scale of Yates and Wai was used for perchloric acid.[15] Dilute acids above pH 1.1 were made up to a constant ionic strength of 0.1 by adding the necessary increments of the sodium salts of the corresponding acids. In the absence of salts, slight shifts in the low wavelength isosbestic points occurred in sulfuric acid as the pH changed. The second pK_a of sulfuric acid was calculated as 2 in preparing such solutions. Normally 15 to 18 spectra were carried out in the pK_2 range to make certain of the end points and isosbestic shifts, and to obtain sufficient data for Hammett plots in the proper range.

Compounds.—Most of the compounds were freshly prepared for this and related studies. Purification was accomplished by recrystallization, and finally by sublimation in many cases. A few old file samples from the Wellcome Research Laboratories were repurified before use.

Acknowledgment.—The authors are deeply indebted to Professor J. F. Bunnett for many helpful suggestions. Discussions with Professors C. A. Bunton and E. Grunwald were also most fruitful. We are very appreciative of the vigorous support which Dr. G. H. Hitchings has given to this program.

Registry No.—**1**, 1004-38-2; **2**, 24867-19-4; **3**, 24867-20-7; **4**, 4940-94-7; **5**, 24867-22-9; **6**, 24867-23-0; **7**, 24867-24-1; **8**, 24867-25-2; **9**, 24867-26-3; **10**, 24867-27-4; **11**, 24867-28-5; **12**, 24867-29-6; **13**, 24867-30-9; **14**, 24867-31-0; **15**, 24867-32-1; **16**, 24867-33-2; **17**, 2227-25-0; **18**, 2878-02-6; **19**, 24867-36-5.

(15) K. Yates and H. Wai, *ibid.*, **86**, 5408 (1964).

The Schmidt Reaction of α-Aralkyl-Substituted Carboxylic Acids[1]

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When 2-phenyl-2-methylhexanoic acid (1) was treated with sodium azide in polyphosphoric acid (ppa), the products of the reaction were aniline (2), 2-hexanone (3), 2-phenyl-1-hexene (4), *trans*-2-phenyl-2-hexene (5), *cis*-2-phenyl-2-hexene (6), and low polymeric material. In order to gain some insight into the route by which aniline was formed, a series of α-di- and trisubstituted acids were examined and found to yield varying amounts of aniline. 2-*p*-Tolyl-2-methylhexanoic acid was reacted to yield *p*-toluidine. The results of these experiments indicate the first step of the reaction to be decarboxylation to an aralkyl cation. In order to substantiate this proposal, the expected intermediates from a "Normal" Schmidt reaction of 1 were prepared by independent syntheses and subjected to rearrangement conditions: the acyl azide **7**, the isocyanate **8**, and the amine **9**, were examined. All of the projected intermediates failed to give aniline on treatment with ppa without azide present. the mechanism is described.

The transformation of carboxylic acids to amines *via* the Schmidt reaction[3] (*i.e.*, hydrazoic acid in sulfuric acid) has been a useful synthetic tool.[4]

The most intriguing example of the anamalous behavior of a carboxylic acid was reported by Arcus and coworkers.[5] 2-Phenyl-2-methylhexanoic acid upon treatment with sodium azide in sulfuric acid gave aniline (55%). They proposed that in the presence of sulfuric acid 2-phenyl-2-methylhexanoic acid (1) was protonated to form the dihydroxycarbonium ion which attacked the nitrogen of hydrazoic acid. This intermediate loses a molecule of nitrogen with the subsequent migration of phenyl to the remaining electron deficient nitrogen to form phenyl isocyanate and the isomeric hexenes. The phenyl isocyanate then decomposes to the observed aniline. However, certain anomalies such as fragmentation[6,7] and isomerization[8] of certain acids in sulfuric acid have limited the usefulness of this reaction.

With the ever growing popularity of ppa as a medium for rearrangements[9] and since it has been reported as a good solvent for the Schmidt reaction of spiro ketones,[10] ppa was used in this study.

In order to clarify the reaction pathway for the apparent phenyl migration reported by Arcus and coworkers[5] and to investigate the fragmentation of acids under Schmidt conditions, (*i.e.*, strong acid media), it was of interest to determine the fate of the possible intermediates (the acyl azide, the isocyanate, the amine, and the olefins) in the Schmidt reaction of acids with or without azide present.

Discussion and Results

When 2-phenyl-2-methylhexanoic acid (1) was heated at 50° with the equivalent of sodium azide for 8 hr in ppa, the products of the reaction were aniline (2), 2-hexanone (3), three isomeric phenyl-substituted hexenes (4–6), and a low polymeric material.[11] None of the isomeric hexenes described by Arcus[5] were observed. Furthermore, the products obtained from acid 1 under these reaction conditions without sodium azide present were the three isomeric phenyl-substituted olefins (4–6) and polymeric material. Since styrene and substituted styrenes have been shown to polymerize in both ppa[12] and concentrated acid[13,14] it was necessary to show that the olefins formed were polymerized under the reaction conditions. The three isomeric phenyl-substituted hexenes prepared independently (*i.e.*, the dehydration of 2-phenyl-2-hexanol) were polymerized in ppa. The results (Table I) show that the polymeric materials were derived from the phenylhexenes.[15] In addition treatment of the polymeric product with sodium azide in ppa did not produce aniline.

Table I

Products Obtained from the Treatment of the Three Olefins with Ppa

Reactant	2-Phenyl-1-hexene (4), %	*trans*-2-Phenyl-2-hexene (5), %	*cis*-2-Phenyl-2-hexene (6), %	Polymer, %
2-Phenyl-1-hexene (4)	None	1.7	None	98.3
trans-2-Phenyl-2-hexene (5)	None	5.4	None	94.6
cis-2-Phenyl-2-hexene (6)	1.3	3.2	34.3[a]	61.2

[a] Interestingly *cis*-2-phenyl-2-hexene (6) is slowest to react and is in good agreement with Table III. A study of the rates of polymerization would be necessary to explain why all three olefins are not observed with compound 5.

(1) Presented in part at the First Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1966.

(2) (a) Abstracted from the Ph.D. Thesis of R. M. Palmere, Seton Hall University, 1966. (b) To whom inquiries should be addressed at Wright State University.

(3) P. A. S. Smith, "Molecular Rearrangements," Vol. I, 1st ed, P. de Mayo, Ed., Interscience, John Wiley & Sons, Inc., New York, N. Y., 1963, pp 483–567 and references therein.

(4) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1953, pp 677–678.

(5) C. L. Arcus, J. Kenyon, and S. Levin, *J. Chem. Soc.*, 407 (1951).

(6) C. Schuerch, Jr., and E. H. Huntress, *J. Amer. Chem. Soc.*, **71**, 2233 (1949).

(7) C. Schuerch, Jr., and E. H. Huntress, *ibid.*, **71**, 2238 (1949).

(8) A. Lundren, *ibid.*, **82**, 3228 (1960).

(9) (a) H. R. Snyder, C. T. Elston, and D. B. Kellom, *ibid.*, **75**, 2014 (1953); (b) H. R. Snyder and C. T. Elston, *ibid.*, **76**, 3039 (1954).

(10) R. T. Conley and B. E. Nowak, *J. Org. Chem.*, **26**, 692 (1961).

(11) While it is convenient to consider the low polymeric material as one component, it was shown by vpc to contain at least three components (having long retention times) which were trapped and found to have virtually identical ir spectra (and quite similar to that of polystyrene) differing only in the relative intensity of various absorptions.

(12) L. A. Paquette and T. A. Phillips, *ibid.*, **30**, 3883 (1965).

(13) W. E. McEwen, M. Gilliland, and B. I. Sparr, *J. Amer. Chem. Soc.*, **72**, 3212 (1950).

(14) M. T. Rosen, *J. Org. Chem.*, **18**, 1701 (1953).

(15) Established by ir spectral comparison of the polymers obtained from the olefin polymerization with those from the Schmidt reaction.

It would appear that on heating the acid **1** with sodium azide in ppa, that there are at least two competing reactions taking place: the first, the addition of azide to the acid (footnote *a*, Table IV); secondly, the decarboxylation of the acid to give olefins which undergo polymerization.

The effect of the preheating time on the products of the Schmidt reaction in ppa (*i.e.*, time of heating before the sodium azide was added) was varied. These results are shown in Table II.

TABLE II

EFFECT OF TIME AT 50° ON 2-PHENYL-2-METHYLHEXANOIC ACID WITH AND/OR WITHOUT SODIUM AZIDE

Pre-heating time, hr	Time with sodium azide, hr	Isomeric olefins, %	Polymer %	Aniline, %
8		10.8	79.7	
8	4	12.6	77.4	0.3[a]
4	8	17.1	67.7	0.6[a]
	8	6.2	34.6	57.7[a,c]
	12	7.6	33.3	54.0[b,c]

[a] Isolated as aniline hydrochloride. [b] Isolated as benzanilide. [c] Interestingly, as the concentration of azide was increased under the reaction conditions noted, the yield of aniline was proportionately greater.

As can be clearly seen by examining the data in Table II, the maximum yield of aniline and polymer are dependent upon the contact time of acid with azide.

Although Arcus and coworkers[5] proposed a phenyl migration to produce an isocyanate intermediate, we thought that perhaps an alternate pathway was also feasible; namely, the reaction may have occurred by an N^+ insertion analogous to that proposed by Lansbury and Colson[16] for hindered ketones or by a cationic intermediate as proposed by Schuerch and Huntress[6] for α-trisubstituted alkyl acids.

When 2-*p*-tolyl-2-methylhexanoic acid was treated with sodium azide under the reaction conditions, *p*-toluidine (73%) was obtained. This experiment eliminated the possibility of an N^+ insertion mechanism. It is reasonable to assume that the first step of the reaction involves the formation of carbonium ion capable of transformation to olefin and to polymer. The attack of azide on this intermediate would be expected to form aniline and ketone since it has been shown[12,17-19] that hydrazoic acid adds to olefins in the presence of sulfuric acid to give aralkyl azides which rearrange to ketones and amines.

Since the observed products were aniline and a ketone as well as olefins, it was necessary to show that the three olefins obtained from decarboxylation of **1** would add azide under Schmidt conditions to give aniline (**2**) and 2-hexanone (**3**). The product distributions from these studies are shown in Table III. From these data it seems realistic to propose that aniline arises from the reaction of azide with the cation, and that this reaction competes with the olefin formation and polymerization processes. Moreover, if the carbonium ion produced

TABLE III

REACTION OF THE THREE ISOMERIC OLEFINS WITH SODIUM AZIDE IN PPA AT 50°

Olefin	Aniline, %	Polymer, %	Unreacted olefin, %
2-Phenyl-1-hexene (**4**)	53.4	45.0	1.2[a]
trans-2-Phenyl-2-hexene (**5**)	43.7	46.0	4.6
cis-2-Phenyl-2-hexene (**6**)	12.9	51.7	35.4[a]

[a] Includes isomeric olefins.

via decarboxylation was phosphorylated, it should be possible to prepare this intermediate from the corresponding 2-phenyl-2-hexanol. This alcohol should give the intermediate which could either eliminate to form the olefins or be attacked by azide to give the aralkyl azide[12,17-19] required for the rearrangement to aniline and ketone. When 2-phenyl-2-hexanol was treated with sodium azide in ppa, only 29% aniline was obtained indicating a competitive polymerization occurring in this case compared with the results during Schmidt reaction of the acid (**1**). Since diphenyl methyl alcohol, when treated in sulfuric acid with sodium azide, gave aniline,[20] and the azide of triphenylcarbinol can be isolated from sulfuric acid,[21] it would appear that the stability of the azide formed from the cation is the controlling factor in this type of rearrangement. With these data in mind, it was decided to study a series of aralkylcarboxylic acids. The groups in the α position were varied in order to determine the yield of aniline as a function of structure. These results are summarized in Table IV and indicate the limitations of this process. In only two cases was the amine from "normal rearrangement" obtained. Phenylacetic acid gave only benzylamine (no aniline could be detected), and 2-phenylhexanoic acid gave 49.2% the expected 1-phenylpentylamine from the "Normal" Schmidt reaction as well as 46.4% aniline. Surprisingly, 1-phenylcyclohexanecarboxylic acid gave 54% aniline and 46% recovered acid. None of the expected amine, 1-phenylcyclohexylamine, was detected.

Assuming that the mechanism of the Schmidt reaction of acids[22] to form amines parallels that of the Curtius rearrangement, then any of the normal intermediates (*i.e.*, acyl azide, isocyanate, or amine) could be an intermediate in the formation of aniline. These intermediates, the acyl azide (**7**), the isocyanate (**8**), and the amine (**9**) (prepared *via* a modification of the Curtius reaction[23]), were treated with ppa with and without azide present (Table V). From the amount of aniline produced, it must be concluded that the α-aralkyl acids are decarboxylated prior to cation formation in ppa rather than rearrangement to any of the expected intermediates as depicted in the sequence of steps in Scheme I.

Experimental Section

Melting and boiling points are uncorrected. Ir spectra were obtained with a Beckman IR-10 grating spectrophotometer. The nmr spectra were determined on a Varian A-60A in deuterio-

(16) P. T. Lansbury and J. G. Colson, *J. Amer. Chem. Soc.*, **84**, 4167 (1962).

(17) Y. Yukawa and K. Tanaka, *Mem. Inst. Sci. Ind. Res., Osaka Univ.*, **14**, 205 (1957); *Chem. Abstr.*, **52**, 2795*g* (1958).

(18) D. R. Nielson and W. E. McEwen, *J. Amer. Chem. Soc*, **76**, 4042 (1954).

(19) L. P. Kuhn and J. Di Domino, *ibid.*, **72**, 5777 (1950).

(20) C. L. Arcus and R. J. Mesley, *Chem. Ind.* (London), 701 (1951).

(21) (a) J. D. Senior, *J. Amer. Chem. Soc.*, **38**, 2718 (1916). (b) S. M. Ege and K. W. Sherk, *ibid.*, **75**, 354 (1953). (c) R. F. Tietz and W. E. McEwen, *ibid.*, **77**, 4007 (1955). (d) J. H. Borps and F. C. Conter, *ibid.*, **77**, 3287 (1955); **78**, 325 (1956). (e) J. C. Water, *ibid.*, **80**, 2328 (1958).

(22) M. S. Newman and H. L. Gildenhorn, *ibid.*, **70**, 317 (1948).

(23) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

Scheme I

Summary of Reaction Steps in the Formation of Aniline from 2-Phenyl-2-methylhexanoic Acid

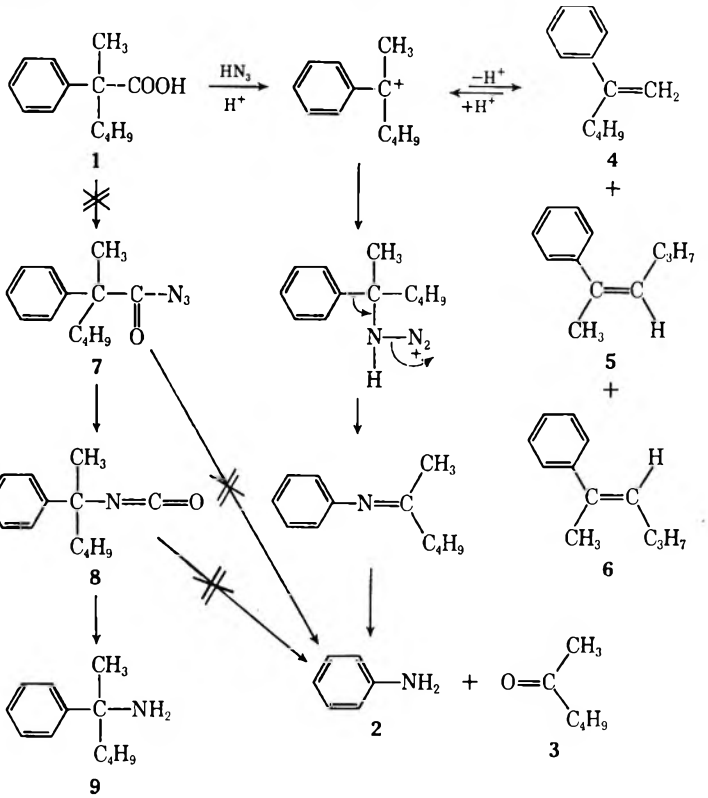
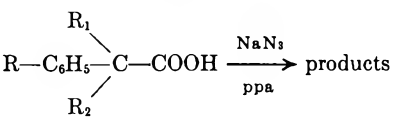


Table IV

Reaction of α-Substituted Phenylacetic Acids with Sodium Azide at 50°



R	R_1	R_2	Registry no.	Recovered acid, %	Olefin, %	Polymer, %	Normal amine, %	Aniline, %
H	H	H	103-82-2	32.3	None	None	67.7	None
H	H	C_4H_9	24716-09-4	None	None	2.3	49.2	46.4
H	H	C_6H_5	117-34-0	95.1	None	None	None	4.0
H	CH_3	C_6H_5	5558-66-7	87.1	None	None	None	12.9
H	C_6H_5	C_6H_5	595-91-5	98.0	None	None	None	None
H	$-CH_2-(CH_2)_3-CH_2-$		1135-67-7	46.0	None	None	None	54.0
H	CH_3	C_4H_9	2955-41-1	0.01[a]	6 3	34.6	None	57.7[b]
CH_3	CH_3	C_4H_9	24716-14-1	None	4 9	21.0	None	73.3[c]

[a] Ir shows a small amount of azide present. [b] Isolated as the hydrochloride. [c] *p*-Toluidine.

Table V

Treatment of Possible Schmidt Intermediates of 2-Phenyl-2-methylhexanoic Acid in Ppa with and without Sodium Azide

Compd	Sodium azide, equiv	Time, hr	Temp, °C	Aniline, %
Acyl azide	...[a]	8	50	None[b,c]
	1	8	50	25.7
Isocyanate	...[a]	8	50	None[b,c]
	1	8	50	44.4
Amine	1	8	50	None[d]

[a] One equivalent of azide is consumed to form the intermediate; therefore, these reactions were carried out without added azide. [b] None (less than 0.1%). [c] Products were olefins and polymer. [d] Only starting amine was isolated.

chloroform or carbon tetrachloride and are referred internally to tetramethylsilane. Vpc was performed on a F & M Model 720 gas chromatograph as follows: 6 ft by 0.25 in. 10% silicone gum nitrile on Chromosorb P, programmed from 60–220° at 20°/min with a helium flow rate of 60 cm³/min; preparative vpc employing Wilkens "auto-prep" using 20 ft by ⅜ in. silicone rubber on Chromosorb W with a helium flow rate of 200 cm³/min, 185° isothermal.

Acids and Esters.—The general procedure of Kenyon, Meyers, and Hauser[24] was employed for the synthesis of the following esters and acids; unless otherwise noted, the vpc of each compound indicated only one component. The ir spectrum was in agreement with the structure.

Ethyl 2-phenylhexanoate (81%):[25] bp 103–105° (2 mm) [lit.[24] 74–76° (0.1 mm)]. *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.35; H, 9.21.

Ethyl 2-(*p*-tolyl)-propionate (81%): bp 116–118° (10 mm) [lit.[24] 121° (11 mm)]. *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 79.77; H, 8.29.

Ethyl 2-phenyl-2-metylhexanoate (75%): bp 132–135° (4

(24) W. G. Kenyon, R. E. Meyers, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

(25) Per cent yield of product obtained.

mm) [lit.[26] 122–125° (4.5 mm)]. *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.46. Found: C, 76.72; H, 9.42.

Ethyl 2-(*p*-tolyl)-2-methylhexanoate (59%): bp 132–134° (2.5 mm). *Anal.* Calcd for $C_{16}H_{24}O_2$: C, 77.33; H, 9.74. Found: C, 77.19; H, 9.82.

2-Phenylhexanoic acid (80%): bp 181–183° (20 mm) [lit.[24] 173–178° (19 mm)]. *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.44; H, 8.39 Found: C, 74.51; H, 8.32.

2-Phenyl-2-methylhexanoic acid (89%): bp 154–156° (4 mm) [lit.[27] 155° (4 mm)]. *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.58; H, 8.81.

2-(*p*-Tolyl)-2-methylhexanoic acid (45%): bp 148–150° (1.0 mm). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.43; H, 9.04.

2,2-Diphenylpropionic acid (86%): mp 173–174° (lit.[28] 173–174°].

1-Phenylcyclohexanecarboxylic acid was prepared by the procedure of Case[29] to give 8.5% desired product: mp 121–122° (lit.[29] 123°).

2-Phenyl-2-hexanol was prepared from *n*-butyl magnesium bromide and acetophenone as described by Conant and Carlson[27] (60%): bp 129–131° (4 mm) [lit.[27,30] 129–130° (4 mm)].

Olefin Synthesis.—The three isomeric phenyl-substituted hexenes, 2-phenyl-1-hexene (4), *trans*-2-phenyl-2-hexene (5), and *cis*-2-phenyl-2-hexene (6), were prepared by the dehydration of 2-phenyl-2-hexanol as described by Mohan and Conley.[30] Each olefin was obtained by preparative vpc. The elemental analysis and refractive indices of each olefin were in good agreement with authentic samples obtained from A. G. Mohan,[30] also, the vpc retention time, ir, and nmr spectra were identical.

Amines and Related Compounds.—Table VI summarizes the products isolated by a modified Curtius[23] rearrangement of the corresponding acids. The following general procedure was used for the synthesis of amines.

TABLE VI

Compd	Bp (obsd), °C (mm)	Bp (lit.), °C (mm)
1-Amino-1-phenylpentane	110–111 (12)	110 (12)[a]
2-Phenyl-2-hexylisocyanate	62–64 (0.5)	
2-Amino-2-phenylhexane	110–112 (2)	127 (18)[b]
1,1-Diphenylethylamine	141–143 (4)	140–142 (4)[c]
1-Phenylcyclohexylamine	84–86 (1.0)	84–89 (1.0)[d]

[a] Krugmann and Co., British Patent 813,524 (May 21, 1951). [b] See ref 5. [c] A. W. Weston and K. E. Hamilton, Jr., Abbott Laboratories, U. S. Patent 2,801,072 (Nov 18, 1958); *Chem. Abstr.*, **53**, 7216*g* (1959). [d] Parke, Davis & Co., British Patent 853,775 (Nov 9, 1960).

2-Phenyl-2-methylhexanoic acid (5.9 g, 0.29 mol) was suspended in 5 ml of water and acetone was added to form a solution. The solution was cooled to 0° and 3.4 g (0.033 mol) of triethylamine in 65 ml of acetone was added, followed by 4.17 g (0.037 mol) of ethyl chloroformate in 15 ml of acetone. The solution was stirred an additional 30 min at 0° after the addition was completed. Sodium azide (2.87 g, 0.043 mol) in 10 ml of water was added dropwise, maintaining the temperature at 0°. After the addition was completed the mixture was stirred for 1 hr, was poured into ice water, and was extracted with ether. The ether portion was dried ($MgSO_4$) and most of the ether was removed at reduced pressure. Since acyl azides are known to decompose violently with heat and shock, some of the ether solvent was allowed to remain. The infrared spectra of 2-phenyl-2-methylhexanoic acid azide showed a characteristic azide band at 2150 (N_3 str) and 1725 cm^{-1} (C=O str).

The solution of acyl azide was diluted with 25 ml of dry toluene and the residual ether was removed *in vacuo*. The solution of acyl azide in toluene was added dropwise to a hot flask equipped with an efficient condenser. After the evolution of nitrogen had ceased (1 hr) the crude product was examined by vpc (93% isocyanate). The 2-phenyl-2-methylhexyl isocyanate distilled at 62–64° (0.05 mm); $n^{21}D$ 1.5021; ir 2250 cm^{-1} (N=C=O stretching frequency); vpc (silicone gum nitrile) showed only one component.

The 2-phenyl-2-methylhexyl isocyanate (4.53 g) was refluxed with 30 ml of 20% aqueous hydrochloric acid for 16 hr. The clear solution was cooled, extracted with ether, and the aqueous portion was evaporated at reduced pressure. The residual semisolid crystallized from ethyl acetate–ether, mp 133–141°.

Recrystallization from ethylacetate–ether gave 2.21 g, mp 141–143° (lit.[8] 144–147°), of the 2-phenyl-2-hexylamine hydrochloride. *Anal.* Calcd for $C_{12}H_{20}NCl$: C, 67.45; H, 9.37; N, 6.57; Cl, 16.61. Found: C, 67.51; H, 9.41; N, 6.61; Cl, 16.73.

The amine hydrochloride was converted to the free amine with sodium hydroxide, 2-phenyl-2-hexylamine, bp 110–112° (2 mm) [lit.[8] 127° (18 mm), lit.[30] 76–80° (0.6–1.0 mm)].

The N-benzoyl derivative was prepared, 2-benzamido-2-phenylhexane, mp 146–147° (lit.[8,30] 146–147°).

The N-acetyl derivative had mp 110–111° (lit.[30] 110–111°).

Schmidt Reactions.—All reactions were carried out in 17–20:1 weight ratio of ppa to reactant. A typical reaction procedure is described. A summary of the data is found in Tables I to V.

2-Phenyl-2-methylhexanoic Acid.—To a solution of 2.07 g (0.01 mol) of 2-phenyl-2-methylhexanoic acid in 40 g of ppa gently stirred at 50° was added 0.650 g (0.01 mol) of sodium azide maintaining the temperature at 50°. The mixture was gently stirred for 8 hr (gas evolution). The flask was removed from the bath, filled with crushed ice, and stirred until the aqueous ppa could be poured into a separatory funnel. The mixture was extracted three times with 50-ml portions of methylene chloride to remove any unreacted acid and neutral products. The methylene chloride extracts were combined and washed successively with 10% sodium hydroxide solution and water. The extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 1.78 g of crude oil. The crude oil was analyzed by vpc (silicone gum nitrile). Six components were trapped and characterized as follows.

First Component.—Retention time 1.3 min (47.7%),[31] identified as 2-hexanone by comparison of its ir spectrum and retention time with that of an authentic sample; the 2,4-dinitrophenylhydrazone, mp 106° (aqueous–alcohol) (lit.[32] 106°), no depression upon admixture with an authentic sample; the semicarbazone, mp 122–124° (lit.[32] 122°).

Second Component.—Retention time 3.2 min (5.1%), characterized as *trans*-2-phenyl-2-hexene by spectral comparison (ir and nmr) with an authentic sample.

Third Component.—Retention time 3.6 min (0.3%), characterized as 2-phenyl-1-hexene from its retention time and peak enhancement with an authentic sample.

Fourth Component.—Retention time 4.0 min (0.9%), characterized as *cis*-2-phenyl-2-hexene from its retention time and peak enhancement with an authentic sample.

Fifth Component.—Retention time 7.0 min (0.5%), unidentified.

Sixth Component.—Retention times 8.3 and 9.1 min (34.5% total), were identified as polymeric materials by their retention times and ir spectral identity with polymeric products from the polymerization of the olefins in ppa.

The sodium hydroxide extract was acidified with hydrochloric acid and extracted with methylene chloride. The methylene chloride was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to give 30 mg (0.01%) of 2-phenyl-2-methylhexanoic acid identified by its ir spectrum. The aqueous ppa portion was made alkaline with solid sodium hydroxide while adding ice chips to maintain the temperature below 25°. The basic solution was extracted with methylene chloride. The extracts were washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to give 0.594 g of crude oil. Vpc analysis of the crude oil (silicone gum nitrile) showed a single component, retention time 3.2 min (57.7%), identified as aniline by comparison of its ir spectrum, retention time, and enhancement of the peak with an authentic sample.

(26) W. G. Kenyon, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, **30**, 2937 (1965).

(27) J. B. Conant and B. H. Carlson, *J. Amer. Chem. Soc.*, **54**, 4048 (1932).

(28) M. T. Bateman, *ibid.*, **49**, 2917 (1927).

(29) F. H. Case, *ibid.*, **56**, 715 (1934).

(30) A. G. Mohan and E. T. Conley, *J. Org. Chem.*, **34**, 3259 (1969).

(31) The yield of component in all cases is based upon amount of crude isolated and the relative abundance of the component obtained from the vpc peak area.

(32) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., p 316.

Derivatization of the crude oil by dissolution in anhydrous ether and treatment with hydrogen chloride yielded 0.694 g (57.5%) of aniline hydrochloride, mp 196–198° (lit.[33] 198°). Mixture melting point determination gave no depression.

In a second identical experiment the aniline (54%) was isolated and characterized as its benzamide derivative. The oil described above was treated with benzoyl chloride in pyridine to give 1.07 g, mp 161–163° (lit.[33] 163°).

(33) I. Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, 1953.

Registry No.—Ethyl 2-(*p*-tolyl)-2-methylhexanoate, 24716-15-2; 2-phenyl-2-hexyl isocyanate, 24716-16-3.

Acknowledgment.—The authors wish to thank J. Alicino of the Squibb Institute for Medical Research in New Brunswick, N. J., for his aid in recording the elemental analysis data, and to Dr. P. L. Valint for a sample of 1-phenylcyclohexanecarboxylic acid.

Proton Nuclear Magnetic Resonance Spectra of Arylmethyl Systems[1]

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The proton nmr spectra of a number of arylmethyl derivatives $ArCH_2X$, where ArH is an alternant aromatic hydrocarbon, have been measured. The differences in chemical shift of the methylene protons appear to be due primarily to ring current effects rather than hyperconjugation.

Since the early days of nmr spectroscopy, much attention has been paid to the factors affecting the chemical shifts of protons attached to atoms in aromatic rings.[3,4] As a result of extensive experimental and theoretical studies, a reasonably consistent picture of such chemical shifts has emerged. This satisfactory situation does not, however, extend to side-chain protons in, *e.g.*, methyl derivatives of such systems, and there has been controversy in such cases concerning the possible role of hyperconjugation.

Fraser and his collaborators[5] measured the nmr spectra of a number of *para*-disubstituted benzene derivatives $XC_6H_4CH_2Y$ and correlated the chemical shifts of the methylene protons using the Hammett relation; they concluded from these correlations that the differences were due to the effect of the substituent X on hyperconjugative interactions between methylene and the ring. On the other hand, Ouellette and van Leuwen[6] interpreted the chemical shifts of methyl in monomethyl derivatives of benzene, naphthalene, anthracene, phenanthrene, and benzo[*a*]anthracene in terms of diamagnetic shielding of the methyl protons by aromatic ring currents; they did not consider the possible role of hyperconjugation, and the monomethyl derivatives of benzo[*c*]phenanthrene showed deviations which they attributed to interference with ring currents due to nonplanarity of the molecule.

The work of Fraser, *et al.*,[5] is not conclusive because substituents containing heteroatoms can exert long-range magnetic shielding effects;[7] the correlation with the Hammett relation could therefore have been fortuitous, particularly in view of the small number of compounds studied in some of their series and the scatter of the Hammett plots. It is also possible that the effects of substituents on ring current could roughly follow the Hammett relation; this possibility cannot be excluded on the basis of their results since these referred only to one ring system.

If, on the other hand, hyperconjugation in compounds of the type $ArCH_3$ is important, one would expect it to vary with the nature of the aryl group. The variations observed by Ouellette and van Leuwen[6] could then have been due to this rather than to magnetic shielding, the correspondence with the latter being due to coicidence. As a rough measure of the conjugation between Ar and CH_3 in $ArCH_3$, one may take the corresponding interaction between Ar and CH_2 in the odd AH (alternant hydrocarbon) $ArCH_2$; this in turn is given approximately by the NBMO (nonbonding MO) coefficient (a_{or}) at the position in Ar adjacent to methylene.[8]

Figure 1 shows a plot of the chemical shifts reported by Ouellette and van Leuwen[6] against a_{or}; there is clearly a reasonable linear relation between the two quantities and the scatter could well be due to the crudity of this procedure for estimating the hyperconjugative interactions in $ArCH_3$. Only four points deviate significantly from the line and these are all for compounds where the methyl is severely hindered, *viz.*, 4-methylphenanthrene (A), 1-methylbenz[*a*]anthracene (B), 12-methylbenz[*a*]anthracene (C), and 1-methylbenzo[*c*]phenanthrene (D). There is evidence that steric compression may lead to significant chemical shifts.[9]

It is particularly striking that the points for the remaining five methylbenzo[*c*]phenanthrenes behave normally in the plot of Figure 1; Ouellette and van Leuwen[6] were forced to neglect them since the observed chemical shifts deviated from their relation calculated on the basis of magnetic shielding by ring currents. They attributed the discrepancy to the known nonplanarity of benzo[*c*]phenanthrene; this, however, seems unconvincing since the angular distortions of the individual rings are too small to influence the π MO's significantly, since the total strain

(1) This work was supported by the Air Force Office of Scientific Research, Grant No. AF-AFOSR-1050-67.

(2) NASA Trainee, 1965–1968.

(3) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959.

(4) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, Oxford, 1965.

(5) R. R. Fraser, C. Reyes-Zamara, and R. B. Swingle, *Can. J. Chem.*, **46**, 1595 (1968).

(6) R. J. Ouellette and B. G. van Leuwen, *J. Org. Chem.*, **34**, 62 (1969).

(7) See M. J. S. Dewar and Y. Takeuchi, *J. Amer. Chem. Soc.*, **89**, 390 (1967), and references cited there.

(8) See M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1969.

(9) See *e.g.*, F. A. Davis and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **90**, 3511 (1968), and references cited there.

TABLE I

CHEMICAL SHIFTS[a] OF SIDE-CHAIN PROTONS IN $ArCH_2X$ SYSTEMS

	X											
	OH[b]		Cl		Br		I		OTS		H	
Ar	τ	Δ_ϕ	τ	Δ_ϕ	τ	Δ_ϕ	τ	Δ_ϕ	τ	Δ_ϕ	τ	Δ_ϕ
Phenyl (a)	5.37	0.00	5.45[c]	0.00	5.57	0.00	5.58	0.00	4.92	0.00	7.68	0.00
2-Naphthyl (b)	5.18	0.19	5.27	0.18	5.38	0.19	5.42	0.16	4.77	0.15	7.54	0.14
2-Phenanthryl (c)	5.12	0.25	5.27	0.18	5.31	0.26			4.72	0.20	7.45[d]	0.23
3-Phenanthryl (d)	5.07	0.30			5.28	0.29			4.65	0.27	7.40[d]	0.28
3-Perylenyl (e)	4.96	0.41[e]									7.42	0.26
2-Pyrenyl (f)	4.88	0.49							4.52	0.40	7.18	0.50
1-Naphthyl (g)	4.88	0.49	4.97	0.48	5.07	0.50	5.13	0.45	4.47	0.45	7.32	0.36
9-Phenanthryl (h)	4.83	0.54			5.03	0.54			4.43	0.49	7.31[d]	0.37
1-Anthryl (i)	4.74	0.63			4.90	0.67						
1-Pyrenyl (j)	4.67	0.70			4.82	0.75					7.20[f]	0.48
9-Anthryl (k)	4.37	1.00	4.42	1.03	4.53	1.04					7.03[c]	0.65

[a] Chemical shifts relative to TMS; concentration 30 mg/0.3 ml in $DCCl_3$ unless otherwise specified; spectra measured with Varian A-60A. [b] Concentration = 2.78×10^{-4} mol in 0.3 ml of $CDCl_3$ + 0.2 ml of acetone-d_6. [c] The Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, Pa. [d] K. D. Bartle and J. A. S. Smith, *Spectrochim Acta*, **23A**, 1689 (1967). [e] Very dilute; spectrum measured on Varian HA-100. [f] Measured in CS_2: E. Clar, B. A. McAndrews, and M. Zander, *Tetrahedron*, **23**, 985 (1967).

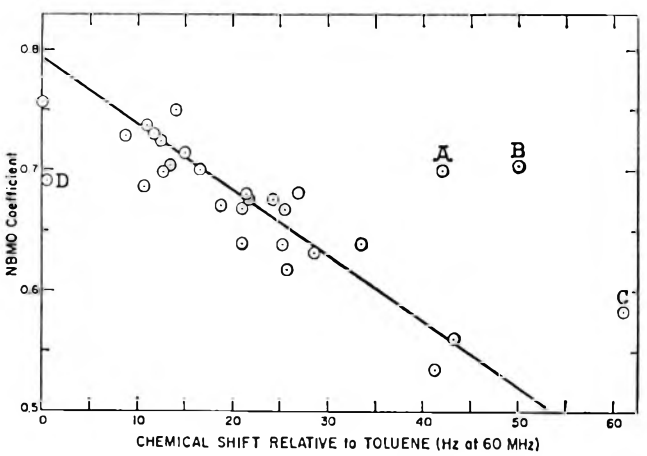


Figure 1.—Plot of chemical shifts of the methyl protons in $ArCH_3$ *vs.* NBMO coefficients (a_{or}) at the methylene carbon in $ArCH_2$.

energy seems to be only about 7 kcal/mol,[10] and since similar strain effects occur in A, B, and C, the points which followed the relation derived by Ouellette and van Leuwen. Their results therefore certainly do not establish unequivocally that the variations in chemical shift of the methyl groups in $ArCH_3$ are due to magnetic shielding rather than hyperconjugation.

In the course of another investigation[11] we had occasion to prepare a number of compounds of the type $ArCH_2X$ where ArH is an alternant aromatic hydrocarbon. As has been pointed out previously,[8] the use of such groups avoids complications due to polar effects since alternant hydrocarbons are nonpolar; any differences in chemical shifts between different members of a given series of compounds $ArCH_2X$, X being constant, must therefore be due solely to the effects of ring currents and/or of hyperconjugation.

Experimental Section

Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected, and nmr spectra were measured with a Varian A-60 spectrometer except in cases indicated where a Varian HA-100 spectrometer was used.

3-Hydroxymethylperylene.—3-Formylperylene (20 g) was added to a stirred solution of sodium borohydride (0.15 g) in tetrahydrofuran (100 ml) and the mixture refluxed for 2 hr. Half the solvent was distilled and the residue poured onto a mixture of crushed ice (300 g) and concentrated hydrochloric acid (300 ml). The resulting solid was collected and crystallized several times from benzene, giving 3-hydroxymethylperylene as a pale yellow powder, mp 175° dec.

Anal. Calcd for $C_{21}H_{14}O$: C, 89.34; H, 5.00. Found: C, 89.11; H, 5.19.

The remaining compounds were prepared according to methods described in the literature. Their melting points and other physical properties agreed with those previously recorded. Full details will be found in a thesis by one of us.[12]

Results and Discussion

Table I lists the chemical shifts for the side-chain protons for the compounds investigated by us. For each group X in $ArCH_2X$, the first column gives the chemical shift of the side-chain protons on the τ scale while the second column shows their values (Δ_ϕ) relative to the benzyl derivative, $PhCH_2X$. The chemical shifts for the methyl derivatives (X = H) show a reasonable correspondence with those of Ouellette and van Leuwen, given that they used a different solvent (DMSO).

The most interesting feature of the data in Table I is the remarkable constancy of the Δ_ϕ values from series to series for a given aryl group. For the two most extensive series, the arylmethyl bromides and the arylcarbinols, the Δ_ϕ values are almost identical even though the spectra were obtained in different solvents. A further conclusion is that although the Δ_ϕ values are reasonably constant for a given aryl in the $ArCH_2X$ (X ≠ H) series, they are consistently smaller in the $ArCH_3$ series; thus Δ_ϕ ranges from 0 for benzyl bromide to 1.04 ppm for 9-anthrylmethyl bromide, whereas the corresponding change in the methyl series amounts to only 0.65 ppm.

One obvious explanation of these results would be based on the magnetic shielding effect of aromatic ring currents; indeed, the chemical shifts in Table I run approximately parallel to those observed[4] for protons attached to corresponding positions in the ring. The latter must of course be due essentially to the magnetic effects of ring currents since there can be no resonance interactions between such a hydrogen atom and the

(10) M. J. S. Dewar and C. de Llano, *J. Amer. Chem. Soc.*, **91**, 789 (1969).

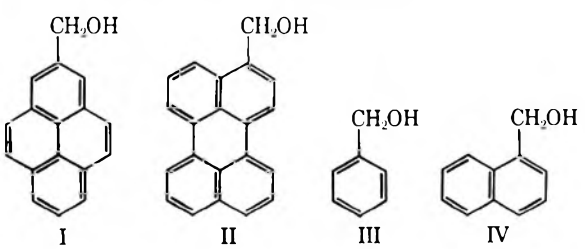
(11) M. D. Bentley and M. J. S. Dewar, work in course of publication.

(12) M. D. Bentley, Ph.D. Dissertation, The University of Texas, 1968.

ring. It is, however, difficult to explain on this basis the difference between arylmethyl derivatives $ArCH_2X$ ($X \neq H$) and the corresponding arylmethanes, for the magnetic environment of the side-chain protons is very much the same in both cases.

We thought at first that this discrepancy might be due to hyperconjugation, the side-chain protons being deshielded by the resulting transfer of charge from the side-chain protons to the ring. This effect should of course depend critically on the dihedral angle of the CH bond in the side chain relative to the ring, and steric effects could well lead to a greater net interaction in compounds of the type $ArCH_2X$ ($X \neq H$) than in $ArCH_3$. An explanation in terms of hyperconjugation also seemed to be supported by the linearity of a plot (Figure 2; points ⊙) of our chemical shifts against corresponding reactivity numbers (*cf.* Figure 1). However, our calculations of the possible effects of ring current indicated that our results might also be explained in terms of magnetic shielding (*cf.* ref 6); so we devised a crucial experiment to distinguish between the two hypotheses.

Calculations of the magnetic shielding of the methylene protons in 2-hydroxymethylpyrene (I) and 3-hydroxyperylene (II), using the Johnson–Bovey tables[13] together with the procedure of Jonathan, Gordon, and Dailey,[14] indicated that the methylene protons in I should be much more deshielded than those in benzyl alcohol (III), while the methylene protons in II should be deshielded to almost the same extent as those in α-hydroxymethylnaphthalene (IV). On the other hand the NBMO coefficients a_{or} corresponding to I and IV are identical, whereas that for II is much smaller than that for IV. If then hyperconjugation is in fact the dominant factor, the methylene protons in I and III should have similar chemical shifts, while the methylene protons in II should appear well downfield of those in IV. Conversely, if magnetic shielding predominates, the signal for the methylene protons in I should appear downfield from that for III, while the signals for II and IV should be almost identical. In this case the point for I should deviate to the right of the line in Figure 2, and the point for II to the left. Furthermore, the conclusions reached in this way are not made ambiguous by steric effects.



The points for I (⊡) and II (△) are also plotted in Figure 1; it will be seen that they deviate markedly from the line and in the directions to be expected if the chemical shifts are indeed due primarily to magnetic shielding rather than hyperconjugation.

It is of course possible that some or all of these effects might be functions of the solvent; this, however, seems unlikely.[6] All the spectra, except those of the carbinols, were measured in fairly dilute (6% w/w) solution, and extrapolation to infinite dilution in one typical case (9-bromomethylphenananthrene) led to a change in chemical shift of only 4.5 Hz. Likewise the change in chemical shift for toluene in chloroform-*d* on passing from 6% solution to infinite dilution is only 1.8 Hz.[15] Changes of this magnitude are far too small to account for the differences in Table I. Moreover the Δ_ϕ values for the bromides and carbinols were almost identical, although the former were measured in 6% w/w solution in chloroform-*d* while the latter were measured at constant molar concentration in a different solvent (acetone-d_6–chloroform-*d*). It seems unlikely that this could have been due to a coincidence.

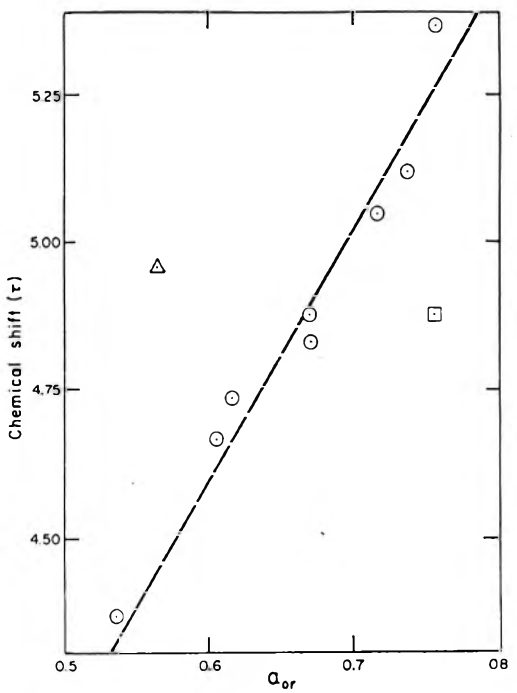


Figure 2.—Plot of $\Delta\phi$ *vs.* a_{or} for arylmethylcarbinols.

Closer examination of Table I shows that the differences in Δ_ϕ between $ArCH_2X$ and $ArCH_3$ are greater the more hindered the aryl group. Thus the differences are negligible for groups of "β-naphthyl" type with both positions *ortho* to the side chain free, are large for groups of "α-naphthyl" type with one *ortho* position blocked by an adjacent ring, and are very large for 9-anthryl where both *ortho* positions are blocked. This suggests very strongly that the differences are conformational in origin, the group X in $ArCH_2X$ being obstructed by adjacent *peri* hydrogens. Steric effects of this kind could influence the side-chain chemical shifts, regardless of whether they are due primarily to hyperconjugation or the effects of aromatic ring currents.

The steric origin of these differences was further supported by studies of the nmr spectra at low temperatures. Thus the methylene protons of 1-naphthylmethyl bromide in acetone–Freon-11 showed a downfield shift of 24 Hz on cooling from 40 to −100°, while the corresponding protons in 2-naphthylmethyl bromide showed only a 12-Hz downfield shift over the same temperature range. This result incidentally indicates that steric effects that force the group X in $ArCH_2X$ out of

(13) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(14) N. Jonathan, S. Gordon, and B. P. Dailey, *ibid.*, **36**, 2443 (1962).
(15) K. D. Bartle and J. A. S. Smith, *Spectrochim. Acta*, **23A**, 1689 (1967).

the plane of the ring shift the methylene signal downfield, and that similar steric effects are present even in compounds of "β-naphthyl" type.

An attempt was made to calculate the effect of such noncoplanarity on the shielding due to ring current by using the Johnson–Bovey tables[13] and the procedure of Jonathan, Gordon, and Dailey,[14] In the case of the arylmethanes, it was assumed that the methyl groups rotate freely, while in $ArCH_2X$ ($X \neq H$) only conformations ranging from those with the C–C–X plane perpendicular to the plane of the ring to those with the C–C–X plane parallel to the plane of the ring, with X *trans* to the *peri* hydrogen, were considered. The results are shown in Table III.

TABLE III

Δ_ϕ VALUES OF SIDE-CHAIN PROTONS IN ArY SYSTEMS

			—CH₂X—	
Ar	Y, $\Delta_{\phi calcd}$	CH_3, $\Delta_{\phi exptl}$	$\Delta_{\phi calcd}$	$\Delta_{\phi exptl}$ (X = OH)
Phenyl	0.00	0.00	0.00	0.00
2-Naphthyl	0.24	0.14	0.17	0.19
1-Naphthyl	0.45	0.36	0.50	0.49
9-Anthryl	1.05	0.65	1.06	1.00

The calculations clearly do not account for the differences between $ArCH_3$ and $ArCH_2X$; however, it could well be that our procedure is simply too crude, assuming as it does that there is *no* interaction between X and an *ortho* hydrogen. The constancy of the Δ_ϕ values for different derivatives $ArCH_2X$ is certainly easier to explain if the effect is due to magnetic shielding, since hyperconjugation should be influenced by the nature of the group X.

As mentioned above, similar arguments have been used by Fraser, *et al.*,[5] to account for the chemical shifts of the methylene protons in *para*-disubstituted benzenes, $X–C_6H_4–CH_2Y$. They analyzed their results in terms of the Hammett relation, obtaining values of ρ for different groups Y ranging from −0.02 to −0.2 ppm/σ. The variations in ρ did not show any correlation with the electronegativity of the atom in Y adjacent to the benzyl group, but seemed to correlate roughly with the size of that atom; Fraser, *et al.*, accordingly attributed the variations in ρ to steric effects, the group X restricting rotation about the $C_6H_4–CH_2$ bond.

These conclusions were, however, based on somewhat inadequate data, the number of compounds of a given type often being small and the linearity of the Hammett plots far from convincing. It is perhaps significant that no such effect was observed in the present work in any of the systems studied, although the range of chemical shifts was much greater (1 *vs.* 0.2 ppm) than in the cases reported by Fraser, *et al.*, and although the possible steric effects in many of our compounds were much greater. We suspect that the small differences observed by Fraser, *et al.*, may well have been due to intermolecular association, particularly in cases where highly polar substituents were present. Fraser, *et al.*, do not seem to have extrapolated their results to infinite dilution, and of course solvent effects, and effects of association, would be relatively much more important in the systems studied by them since the substituent chemical shifts were so small.

Registry No.—3-Hydroxymethylperylene, 24471-30-5. Table I—a (X = OH), 100-51-6; a (X = Cl), 100-44-7; a (X = Br), 100-39-0; a (X = I), 620-05-3; a (X = OTs), 1024-41-5; a (X = H), 108-88-3; b (X = OH), 1592-38-7; b (X = Cl), 2506-41-4; b (X = Br), 939-26-4; b (X = I), 24515-49-9; b (X = OTs), 24471-37-2; b (X = H), 91-57-6; c (X = OH), 2606-54-4; c (X = Cl), 885-21-2; c (X = Br), 2417-66-5; c (X = OTs), 24471-41-8; c (X = H), 2531-84-2; d (X = OH), 22863-78-1; d (X = Br), 24471-44-1; d (X = OTs), 24471-45-2; d (X = H), 832-71-3; e (X = OH), 24471-30-5; e (X = H), 24471-47-4; f (X = OH), 24471-48-5; f (X = OTs), 19127-77-6; f (X = H), 3442-78-2; g (X = OH), 4780-79-4; g (X = Cl), 86-52-2; g (X = Br), 3163-27-7; g (X = I), 24471-54-3; g (X = OTs), 5751-30-4; g (X = H), 90-12-0; h (X = OH), 4707-72-6; h (X = Br), 24471-57-6; h (X = OTs), 24471-58-7; h (X = H), 883-20-5; i (X = OH), 22863-81-6; i (X = Br), 24463-14-7; j (X = OH), 24463-15-8; j (X = Br), 2595-90-6; j (X = H), 2381-21-7; k (X = OH), 1468-95-7; k (X = Cl), 24463-19-2; k (X = Br), 2417-77-8; k (X = H), 779-02-2.

Effects of Central and Terminal Groups on Nematic Mesophase Stability[1]

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Sixteen liquid crystalline *p*-phenylene esters of hydroquinone and *para*-substituted phenyl esters of terephthalic acid have been synthesized. Most of them exhibit very broad nematic ranges and high transition temperatures. The effects of structural changes on mesophase stability are also discussed.

Since nematic liquid crystals[2] are being used as solvents for nmr,[3] esr,[4] uv,[5] and gas chromatography[6,7] studies, there is a need for suitable mesomorphic substances with wide mesomorphic temperature ranges and favorable glass-forming tendencies. We were also interested in the effect of changing the central and terminal groups in a mesomorphic molecule on the stability of its nematic mesophase.

One way of getting wider nematic ranges is to mix two miscible mesomorphic components with approximately the same mesophase–isotropic transition points. In most cases the solid–mesophase transition point is lowered, while the mesophase–isotropic point varies only slightly. The *p*-phenylene esters of the *p*-alkoxybenzoic acids (I)[8] were suitable for both our purposes since they exhibit long mesophases and since the terminal and central groups can be easily modified. We have accordingly made a number of new compounds of this type and studied their ability to form mesophases, both alone and as mixtures with I. The modifications made were inversion of the carboxylate groups in I, giving II, and substitution of various terminal groups in place of alkoxyl.

Experimental Section

***para*-Substituted Benzoic Acids.**—Ethyl *p*-hydroxybenzoate was converted to ethyl *p*-alkoxybenzoate with the appropriate alkyl halide, and the esters were saponified to the corresponding acids by the method of Gray and Jones.[9] The transition points agreed well with those of Gray and Jones. The *p*-fluoro-, *p*-nitro-, and *p*-chlorobenzoic acids were obtained commercially and the *p*-carbethoxybenzoic acid was obtained from Dr. J. P. Schroeder, University of North Carolina at Greensboro. The preparation of the 1,4-bicyclo[2.2.2]octylene esters of *p*-*n*-hexyloxy- (III) and *p*-*n*-octyloxy- (IV) benzoic acids and the *trans*-1,4-cyclohexylene ester of *p*-*n*-hexyloxybenzoic acid (V) have been reported elsewhere.[10]

***para*-Substituted Benzoyl Chlorides.**—The acid chlorides were prepared from the acids by treatment with thionyl chloride. The excess thionyl chloride was flashed off to give, as the residue, the acid chloride.

***p*-Phenylene Esters of *para*-Substituted Benzoic Acids (I).**—Typically, a solution of hydroquinone (0.03 *m*) and dry pyridine (50 ml) was added to a solution of dry pyridine (50 ml) and *p*-alkoxybenzoyl chloride (0.09 *m*). The mixture was stirred at room temperature for 24 hr and then acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water, and slurried for 4 hr in 500 ml of 5% sodium bicarbonate solution. The solution was then filtered and the solid ester was recrystallized from a suitable solvent. The properties of the pure products are presented in Table I.

***para*-Substituted Phenols.**—The *p*-*n*-hexyl- and *n*-heptylphenols were prepared by the method of Klarmann, *et al.*[11] The two synthesized phenols exhibited the following melting points: *p*-*n*-hexyloxyphenol, mp 46–48° (lit.[10] 48°); *p*-*n*-heptyloxyphenol, mp 52–58° (lit.[10] 60°). All other *p*-alkoxyphenols and *p*-fluoro-, *p*-nitro-, *p*-chloro-, and *p*-carbethoxyphenols were obtained commercially.

***para*-Substituted Phenyl Esters of Terephthalic Acid (II).**—Typically, a solution of *p*-alkoxyphenol (0.042 *m*), terephthaloyl dichloride (0.014 *m*), and 100 ml of dry pyridine were stirred for 24 hr at room temperature. The solution was then acidified with dilute hydrochloric acid, and the precipitate was filtered off, washed with ethanol, and recrystallized from a suitable solvent. The properties of the pure products are presented in Table II.

Phase Diagrams.—Mixtures of the two components in known proportions were prepared by fusion and rapid cooling. The transition temperatures of the sample were then obtained both with a polarizing microscope and with a capillary melting point apparatus. The transitions reported are the temperatures at which solid or mesophase have completely disappeared. In the phase diagrams, ⊡ denotes the solid → nematic transition and ⊙ denotes the nematic → isotropic transition. The results are tabulated in Table III.

Melting Points.—Transition temperatures were determined both with a Thomas–Hoover capillary melting point apparatus and with a Leitz Ortholux II polarizing microscope fitted with a heating stage. All melting points are corrected.

Analyses.—Elemental microanalyses were performed by Alfred Bernhardt Microanalytical Laboratories and Galbraith Laboratories.

Results and Discussion

The *p*-phenylene esters of the *para*-substituted benzoic acids provide an excellent system for the study of structural effects on mesophase stability because they are so versatile. We have already used[10] this system to study the role of benzene rings on mesophase stability, and we have now extended these investigations to the role of the terminal groups and the effect of inverting the central carboxyls.

Two homologous series of esters were prepared, *i.e.*, the *p*-phenylene bis-*p*-alkoxybenzoates (I with X = *n*-alkoxy) and the di-*p*-alkoxyphenyl terephthalates (II with X = *n*-alkoxy). All these compounds showed nematic mesophases;[12] the nematic → liquid transition

(1) This work was supported by the U. S. Air Force Office of Scientific Research through Grant No. AF-AFOSR-1050-67.

(2) G. W. Gray, "Molecular Structure and Properties of Liquid Crystals," Academic Press, New York, N. Y., 1962.

(3) G. R. Luckhurst, *Quart. Rev. Chem. Soc.*, **22**, 179 (1968); A. Saupe and G. Englert, *Phys. Rev. Lett.*, **11**, 462 (1963); L. C. Snyder and E. W. Anderson, *J. Amer. Chem. Soc.*, **86**, 5023 (1964); J. C. Rowell, W. D. Phillips, L. R. Melby, and M. Panar, *J. Chem. Phys.* **43**, 3442 (1965).

(4) S. H. Glarum and J. H. Marshall, *ibid.*, **46**, 55 (1967); A. Carrington and G. R. Luckhurst, *Mol. Phys.*, **8**, 401 (1964).

(5) E. Sackmann, S. Meiboom, and L. C. Snyder, *J. Amer. Chem. Soc.*, **90**, 3567 (1968).

(6) (a) M. J. S. Dewar and J. P. Schroeder, *ibid.*, **86**, 5235 (1964); (b) *J. Org. Chem.*, **30**, 3485 (1965).

(7) H. Kelker, *Z. Anal. Chem.*, **198**, 254 (1963).

(8) M. J. S. Dewar and J. P. Schroeder, *J. Org. Chem.*, **30**, 2296 (1965).

(9) G. W. Gray and B. Jones, *J. Chem. Soc.*, 4179 (1953).

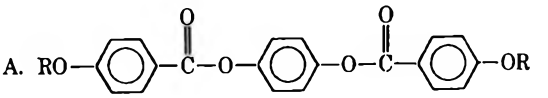
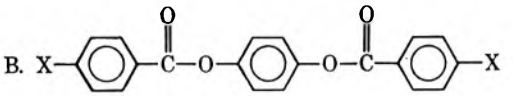
(10) M. J. S. Dewar and R. S. Goldberg, *J. Amer. Chem. Soc.*, **92**, 1582 (1970).

(11) E. Klarmann, L. W. Gatyas, and V. A. Shternov, *ibid.*, **54**, 298 (1932).

(12) We saw no indication of smectic phases under the polarizing microscope; however, Dr. J. L. Fergson has told us that he has detected enantiotropic smectic–nematic transitions in Ig and Ih, and monotropic one in If, using DTA. Since our primary concern was with the stabilities of nematic mesophases and, since DTA equipment is not available here, we are reporting our results in their original form. Since the smectic–nematic transition in If is monotropic, it seems very unlikely that any of the lower esters show stable smectic phases.

TABLE I

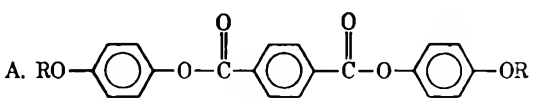
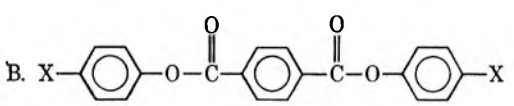
LIQUID CRYSTALLINE *p*-PHENYLENE ESTERS OF *para*-SUBSTITUTED BENZOIC ACIDS

Compd no.	R or X	Recrystn solvent	Yield, %	Mp, °C	Nematic → liquid transition, °C	% C Calcd	% C Found	% H Calcd	% H Found
									
Ia	CH_3	Dioxane	80	213[a,b]	297[c]	69.84	69.90	4.79	4.85
Ib	C_2H_5	EtOAc	33	226	287	70.93	70.75	5.46	5.46
Ic	n-C_3H_7	EtOAc	47.2	175	249	71.87	71.51	6.03	6.11
Id	n-C_4H_9	EtOAc	57	153[d]	241[e]	72.71	72.44	6.54	6.53
Ie	n-C_6H_{13}	Hexane	63	121.5[f]	211	74.10	74.18	7.39	7.48
If	n-C_7H_{15}	Hexane	55	121	198[f]	74.70	74.91	7.74	7.82
Ig	n-C_8H_{17}	Hexane	63.9	118	192	75.23	75.15	8.07	8.09
Ih	n-$C_{10}H_{21}$	Hexane	48.7	122	178	76.15	76.30	8.62	8.63
									
Ii	Cl	EtOAc	65.9	226	246	62.04	61.79	3.12	3.02
Ij	CO_2Et	EtOAc	48.0	203	242	67.53	67.37	4.80	4.92
Ik	NO_2	Dioxane	67.5	260	266	58.83	58.62	2.96	3.12
Il	F	EtOAc	68.3	210[g]		67.80	67.89	3.39	3.60

[a] Obtained from Dr. J. P. Schroeder, University of North Carolina at Greensboro. [b] Lit. 222,[8] 212° [K. Nakazawa, S. Matsuura, and S. Baba, *J. Pharm. Soc. Jap.*, 74, 498 (1954)]. [c] Lit.[8] 300°. [d] Lit.[8] 156°. [e] Lit.[8] 253°. [f] Dr. J. P. Schroeder has confirmed these values which differ from those of ref 8. [g] No mesophase.

TABLE II

LIQUID CRYSTALLINE *para*-SUBSTITUTED PHENYL ESTERS OF TEREPHTHALIC ACIDS

Compd no.	R or X	Recrystn solvent	Yield, %	Mp, °C	Nematic → liquid transition, °C	% C Calcd	% C Found	% H Calcd	% H Found
									
IIa	CH_3	Dioxane	57.5	205	277	69.84	69.70	4.79	4.74
IIb	C_2H_5	EtOAc	62.3	216	266.5	70.93	71.02	5.46	5.58
IIc	n-C_3H_7	EtOAc	70.0	198	238	71.87	72.08	6.03	6.17
IId	n-C_4H_9	EtOAc	58.6	183	229	72.71	72.51	6.54	6.61
IIe	n-C_6H_{13}	EtOAc	52.7	161	201	74.10	73.94	7.39	7.31
IIf	n-C_7H_{15}	EtOAc	49.0	153	188	74.70	74.58	7.74	7.63
									
IIg	Cl	EtOAc	69.0	195	226	62.04	62.28	3.12	3.17
IIh	CO_2Et	EtOAc	85.6	191	235	67.53	67.65	4.80	4.72
IIi	NO_2	DMSO–H_2O	39.4	242[a]		58.83	58.76	2.96	3.05
IIj	F	EtOAc	57.5	226[b]		67.80	67.77	3.39	3.54

[a] Monotropic nematic mesophase at 227°. [b] No mesophase.

temperatures are plotted as a function of chain length in Figures 1 and 2. It will be seen that in each case the points lie on two different curves, one for alkyl groups with an even number of carbon atoms, the other for those with an odd number. In each case the curve for even alkyl groups is the higher, and the curves for the *p*-phenylene esters (I) both lie higher than the corresponding ones for the *p*-alkoxyphenyl terephthalates (II), implying that for each pair of analogs the isomer I forms the more stable mesophase.

As the alkyl chain in a compound of this type is lengthened, the stability of the nematic mesophase should be affected in at least four different ways.[13] First, the alkyl group will act as a diluent, increasing the mean separation between molecules and so likewise the separation between them; this will in turn reduce the anisotropy of the intermolecular forces and so make the mesophase less stable. Secondly, the increase in size of the polar terminal groups will likewise reduce the attractions between them. Thirdly, the increase in length of the molecule will lead to an increase in its geometrical anisotropy. Fourthly, the overall polar-

(13) G. W. Gray, *Mol. Cryst.*, 1, 33 (1966).

TABLE III

SOLID–MESOPHASE (TOP) AND NEMATIC–ISOTROPIC (BOTTOM) TEMPERATURES FOR BINARY SYSTEMS[a]

Components		Mol %, component A											Eutectic	
A	B	0	10	20	30	40	50	60	70	80	90	100	Mol % of A	Temp, °C
Ia	IIa	205	203	199	195	190	188	195	201	205	211	213		184
													47.3	
		277	279	281	283	285	287	289	291	293	295	297		286
Ib	IIb	216	213	210	205	200	196	205	212	218	223	226		194
													48.0	
		266.5	268.5	270.5	272.5	274.5	276.5	279	281	283	285	287		276
Ic	IIc	198	196	192	185	177	167	159	163	167	171	173.5		157
													56.9	
		238	239	240	241	242	243	244	245	246	247	248		244
Id	IId	183	181	178	175	172	165	155	144	145	152	153		137
													73.8	
		229	230	231.5	233	234	235	236	237	238.5	240	241		238
Ie	IIe	161	159	156	152	147	141	135	126	117	119	121.5		113
													84.1	
		201	202	203	204	205	206	207	208	209	210	211		209.5
If	IIf	153	151	150	148	145	140	131.5	124	115	117	121		112
													82.3	
		188	189	190	191	192	193	194	195	196	197	198		196
Ii	IIg	195	193	189	180	183	193	201	209	216	221	226		174
													33.3	
		226	228	230	232	234	236	238	240	242	244	246		232.5
IIa	IIj	226	224	220	216	207	202	203	204	204.5	205	205		201
													45.4	
						215	226	236	246	256.5	267	277		221
Ia	Il	210	207	202	196	188	192	201	207	210	212	213		182
													43.5	
			209	217	227	237	247	257	267	277	287	297		241
III	V	122	121	119	115	107	111	123	131	136	139	141		102
													44.6	
		136	140	145	149.5	155	160.5	166	171.5	177	183.5	190.5		157
IV	Ig	118	117	115	110.5	104	95	99	102	104.5	108	119		92
													52.7	
		192	190	188	185.5	183.5	181.5	179	177	175	173	171		181

[a] The melting points of the pure compounds are direct experimental values; the other temperatures were read from phase diagrams.

izability should increase with increasing molecular size. The first two factors should lead to a decrease in mesophase stability with increasing size of alkyl, the latter two to an increase. In the present case, however, the last two factors should be relatively unimportant since *n*-alkyl groups are flexible and only weakly polarizable; this explains why the nematic → liquid transition temperature decreases with increasing size of the alkyl group.

The stability of the mesophase should be greater, the greater the lateral adhesion of the rod-shaped molecules in question; this in turn should be greater, the greater the polarity and/or polarizability of the central parts of the rod-shaped molecule. In the *p*-phenylene *p*-alkoxybenzoates (I) there is mutual conjugation between the alkoxy and carboxy groups; this should increase the polarity of the carbonyl oxygen and so help to stabilize the mesophase. In the *p*-alkoxyphenyl terephthalates (II) such mutual conjugation is lacking; this could explain why, in each pair of isomers, I has the higher transition temperature.

We next extended our studies to analogous compounds I and II in which the terminal alkoxy groups were replaced by nitro-, chloro-, fluoro-, and ethoxycarbonyl. All these formed mesophases except the fluoro derivatives; here the virtual nematic → liquid transition temperatures were found by extrapolation[10] from phase diagrams for binary mixtures with the corresponding methoxy derivatives (Figures 3 and 4). In each case, the nematic → liquid transition lines were accurately linear; so the transition temperatures can be deduced with reasonable confidence. Table IV compares the transition temperature for compounds I and II with various terminal groups.

TABLE IV

NEMATIC → LIQUID TRANSITION TEMPERATURES (°C)

Compd	X = OMe	F	Cl	COOEt	NO_2
I	297	199	246	242	266
II	277	174	226	235	227

It will be seen that the isomers of series I again have higher transition temperatures than those of series II; this can also be rationalized in the terms indicated above. Thus mutual conjugation between an electron-releasing terminal group and the central carboxyl should stabilize the mesophase in the case of I but have little effect on II, whereas electron-withdrawing groups should have little effect on I but selectively destabilize the mesophase in II, for, in the latter case, mutual conjugation between the substituent and the oxygen atom *para* to it should make the latter positive and so reduce the resonance interactions between it and carbonyl. The net effect will be to make the carbonyl group less polar, and the arguments given above suggest that this

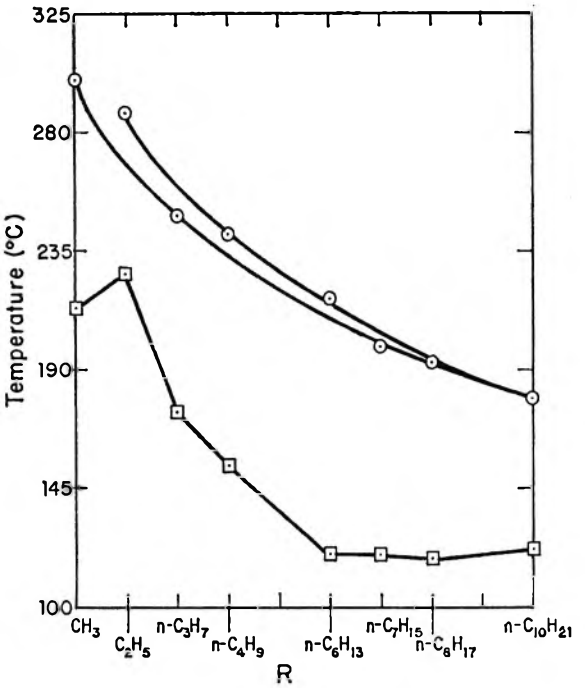


Figure 1.—Phase transition temperatures for the system of the *p*-phenylene esters of *p*-alkoxybenzoic acid.

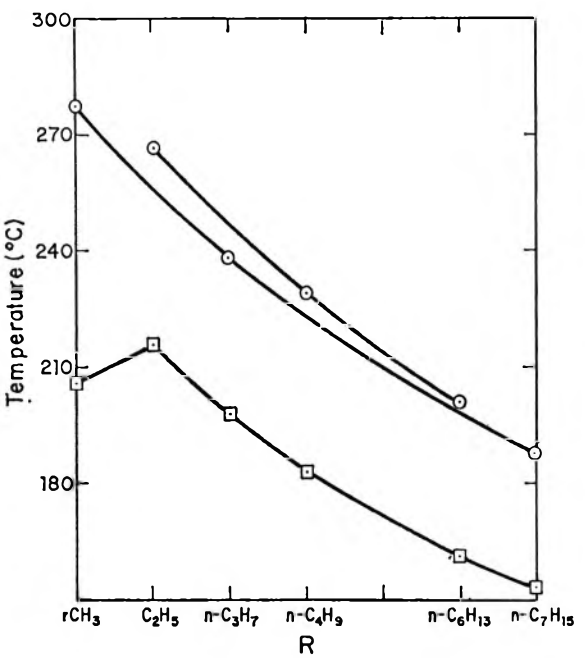


Figure 2.—Phase transition temperatures for the system of the *p*-alkoxyphenyl esters of terephthalic acid.

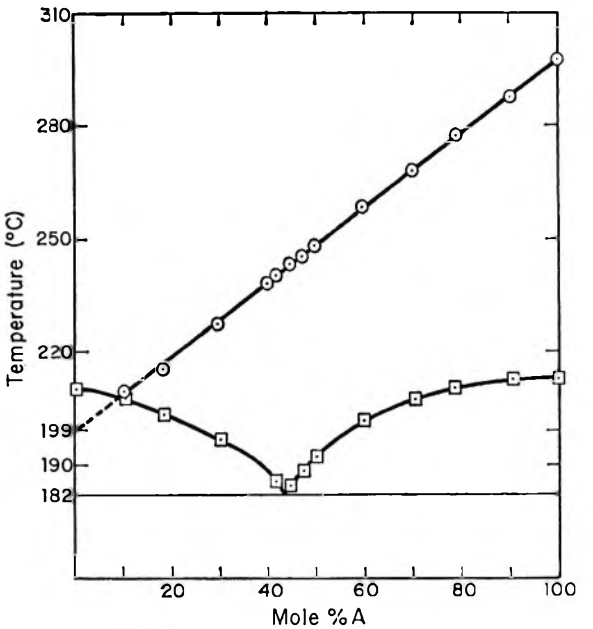


Figure 3.—The phase diagram for the system of *p*-phenylene-di-*p*-anisic ester (A) and *p*-phenylenedi-*p*-fluorobenzoic ester.

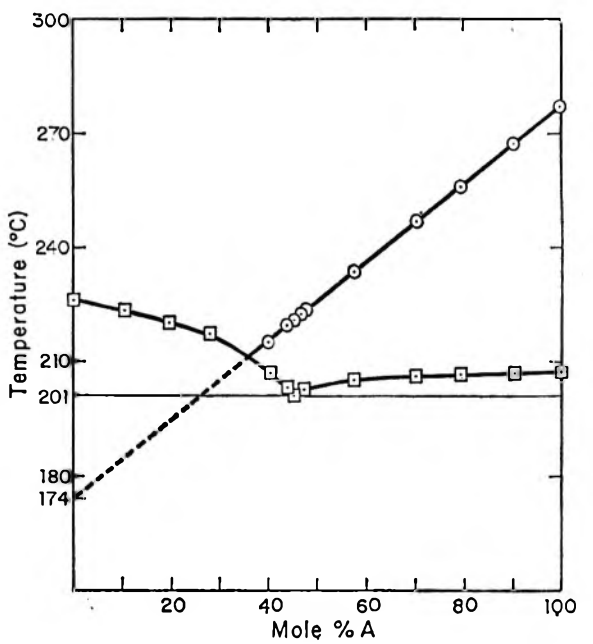


Figure 4.—The phase diagram for the system of di-*p*-methoxyphenyl terephthalate (A) and di-*p*-fluorophenyl terephthalate.

should lead to destabilization of the mesophase. Note that the difference in transition temperature between I and II is the same for the three −E substituents (MeO, F, Cl), but much less for COOEt and much more for NO_2. Ethoxycarbonyl is a weakly +E substituent which will probably have little effect on II; here the transition temperatures for I and II are quite similar. However, the very powerful +E nitro group should have a very large effect on II; the difference in transition temperature is therefore about double the value for MeO, Cl, or F.

The relative effects of the groups can also be rationalized in similar terms. The mesophase stability would be expected to depend on the polarity of the terminal groups as well as that of the central ones; in the case of −E substituents, the net polarity of the terminal group depends on two opposing factors, *i.e.*, the polarity of the σ bond (which makes the terminal group negative) and conjugation with the ring (which makes it positive). In the case of a strongly −E group, one might expect the net charge on the terminal group to be positive owing to the mesomeric interaction. In this case the net charge should be less for fluorine or chlorine than methoxyl since fluorine and chlorine are more electronegative than oxygen and exert smaller −E effects. The fact that chlorine lowers the transition temperature less than fluorine can also be rationalized on this basis, for chlorine has so little tendency to form π bonds that the net polarity of CCl (here $C^{\delta+} - Cl^{\delta-}$) may be greater than that of CF (where the σ and π polarities

may almost cancel). The transition temperatures for X = Cl or F in I or II are therefore lower than for X = MeO. On the other hand ethoxycarbonyl is a bulky group with relatively low +E activity; such a group should tend to lower the transition temperature for geometrical reasons. The nitro group is a very polar group with strong +E activity; in the case of I, where +E activity is irrelevant, the polarity of nitro leads to a relatively large transition temperature. However, in the case of II, the +E activity of nitro leads to strong mutual conjugation with the *para* oxygen and so brings about a large decrease in the transition temperature.

These arguments suggest that the polarity of the groups concerned is the dominant factor; however, polarizability may also play a role. Thus, chlorine is more polarizable than fluorine; this could account for the fact that chlorine has the smaller destabilizing effect on the mesophase.

Mixed Liquid Crystals.—When an unsymmetrical molecule is dissolved in a nematic liquid crystal, it tends to orient itself in the unsymmetrical environment; for this reason liquid crystals offer interesting possibilities as solvents for spectroscopic studies, in particular by nmr.[3] In order to extend this technique to other fields of spectroscopy, it would be desirable to have a liquid crystalline medium that could be supercooled to a glass; it would also be advantageous to have as solvent some material which retained liquid crystallinity over a wide temperature range. One obvious way of achieving this is to use eutectic mixtures of materials forming liquid crystals, for, if the molecules in question are similar in shape, the nematic → liquid transition line is usually straight and the temperature range of the nematic form consequently greater for the eutectic mixture than for either component.

The isomers I and II obviously provide a very favorable example for this purpose and we have accordingly studied a number of binary systems of this type (Table III); a typical example is shown in Figure 5. Mixtures of this kind show relatively long mesophases and they have the further advantage over materials such as anils or azoxy compounds of being thermally and chemically stable. Such mixtures may prove of value in glpc for the separation of position isomers.[6]

We hoped that mixtures of our esters might be persuaded to form glasses since they supercool readily; thus the nematic → liquid transition of II (X = NO_2) could be observed quite easily in supercooled II, 15° below the melting point. Glasses of this kind could be very useful in spectroscopy (*cf.* ref 5); unfortunately, none of the systems studied could be converted to glasses even by very rapid quenching in liquid nitrogen.

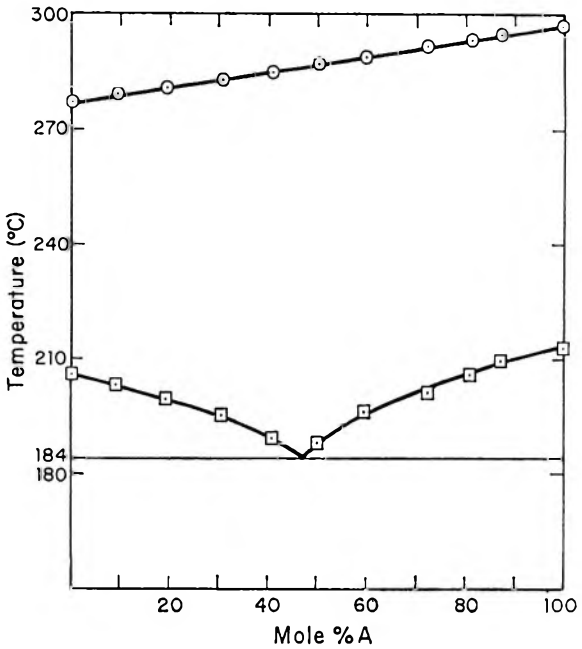


Figure 5.—The phase diagram for system of the *p*-phenylenedi-*p*-anisic ester (A) and di-*p*-methoxyphenyl terephthalate.

Registry No.—Ia, 1962-76-1; Ib, 24706-93-2; Ic, 24704-16-3; Id, 1818-98-0; Ie, 1818-99-1; If, 1819-00-7; Ig, 24706-96-5; Ih, 24704-18-5; Ii, 5411-00-7; Ij, 1819-02-9; Ik, 24706-98-7; Il, 24706-99-8; IIa, 24707-00-4; IIb, 24761-13-5; IIc, 24704-20-9; IId, 24707-01-5; IIe, 24707-02-6; IIf, 24728-02-7; IIg, 24707-03-7; IIh, 24707-04-8; IIi, 3838-05-9; IIj, 24707-06-0; III, 24707-07-1; IV, 24707-08-2; V, 24704-21-0.

Acknowledgment.—We are grateful to Dr. J. L. Ferguson for telling us his unpublished observations of smectic phases in If, Ig, and Ih.

Reductions with Metal–Ammonia Combinations. II. Monothioacetals and Monothioketals. A Synthesis of Alkoxy Mercaptans[1a]

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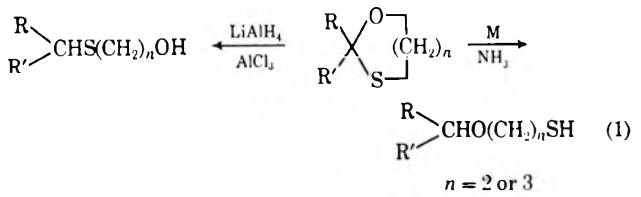
The reduction of oxathiolanes and oxathianes with metal–liquid ammonia combinations gives rise to β- and γ-alkoxy mercaptans. Twenty-six cases have been studied; yields are good for all oxathianes and most oxathiolanes (except those with very simple 2-alkyl groups) when the metal is calcium.

In previous papers[2] the hydrogenolysis of monothioacetals and monothioketals by "mixed hydride"[3] (lithium aluminum hydride–aluminum chloride in a 1:4 ratio) in ether solution was described.[4] Reduction of 1,3-oxathiolanes and 1,3-oxathianes leads to β-hydroxyethyl and γ-hydroxypropyl sulfides, respectively[2a] (eq 1), while 2-tetrahydrofuranyl and 2-tetrahydropyranyl thioethers yield δ-hydroxybutyl and ε-hydroxypentyl sulfides, respectively.[2b] The reaction involves selective cleavage of the C–O bond.



(1)

It is evident that selective cleavage of the C–S bond of 1,3-oxathiolanes and 1,3-oxathianes (eq 1) would provide a convenient route to β-alkoxyethyl and γ-alkoxypropyl mercaptans, respectively. The use of metal–ammonia solutions to cleave C–S bonds seemed promising in this regard, since it has long been known in the literature[5] as being of great importance in the removal of S-protective groups, especially in peptide synthesis.[6]

There are several reports in the literature regarding treatment of dithiolanes with metal–ammonia solutions. For the most part such treatment leads to complete desulfurization[7] or to more complicated reactions.[8] Miles and Owen, however, have reported the selective cleavage of 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolane to 2-isopropylthio-3-hydroxypropyl mercaptan.[9] While this work was in progress,[10] Brown, Iqbal, and Owen[11] reported the selective reduction of a number of other 1,3-dithiolanes to β-mercaptoethyl sulfides and the selective reduction of 2,2-dimethyl-*trans*-4,5-cyclohexano-1,3-oxathiolane to *trans*-2-isopropoxycyclohexanethiol. In contrast, Pinder and Smith have found the reduction of 2-phenyl-2-methyl-1,3-oxathiolane with sodium in liquid ammonia to give ethylbenzene.[12]

Scope

We have found that metal–ammonia reduction of 1,3-oxathiolanes and 1,3-oxathianes (ethylene and trimethylene monothioketals and -acetals) is a fairly general preparative method for β- and γ-alkoxy mercaptans as it involves selective cleavage of the acetal C–S bond (eq 1). The 1,3-oxathiolanes were reduced both with calcium and sodium in liquid ammonia; the compounds reduced and the yields of reduction products obtained are shown in Tables I and II, respectively. Table I also includes the properties of the products. The data for the reduction of 1,3-oxathianes are summarized in Table III; this reduction proceeds more slowly than that of the oxathiolanes.

The starting materials used in this study were prepared from the corresponding aldehydes and ketones and appropriate hydroxy mercaptan in the presence of an acid catalyst.[2a,13] 3-Hydroxypropyl mercaptan was prepared by the method of Clinton and coworkers.[14] In Table V (see Experimental Section) are listed all new starting materials prepared in the present investigation. Configurational assignments to the diastereoisomeric monothioketals obtained in this work have been discussed elsewhere,[2a,15,16] as have the nmr spectra of a number of the oxathiolanes listed in Table V.[17] Reduction products were characterized by ir and nmr spectra; some of them (Table I) were known compounds.[18]

In accord with the report of Pinder and Smith,[12] we have found that 1,3-oxathiolanes carrying 2-phenyl

(1) (a) E. L. Eliel and T. E. Hoover, *J. Org. Chem.*, **24**, 938 (1959), is considered paper I in this series; (b) from the Ph.D. Dissertation of T. W. Doyle, University of Notre Dame, 1966; (c) Charles Bernard McCanna Fellow, 1964–1966.

(2) (a) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962); (b) E. L Eliel, B. E. Nowak, and R. A. Daignault, *J. Org. Chem.*, **30**, 2448 (1965).

(3) E. L. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961); M. N. Rerick in "Reduction," R. L. Augustine, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, Chapter 1.

(4) See also B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **41**, 2671 (1963).

(5) F. E. Williams and E. Gebauer-Fuelnegg, *J. Amer. Chem. Soc.*, **53**, 352 (1931); R. C. Krug and S. Tocker, *J. Org. Chem.*, **20**, 1 (1955); W. E. Truce, D. P. Tate, and D. N. Burdge, *J. Amer. Chem. Soc.*, **82**, 2872 (1960); W. E. Truce and J. J. Breiter, *ibid.*, **84**, 1621 (1962).

(6) R. H. Sifferd and V. du Vigneaud, *J. Biol Chem.*, **108**, 753 (1935); V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts, and P. G. Katsoyannis, *J. Amer. Chem. Soc.*, **76**, 3115 (1954).

(7) L. A. Stocken, *J. Chem. Soc.*, 592 (1947); R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Amer. Chem. Soc.*, **80**, 4604 (1958); N. S. Crossley and H. B. Henbest, *J. Chem. Soc.*, 4413 (1960); R. D. Stolow and M. M. Bonaventura, *Tetrahedron Lett.*, 95 (1964).

(8) Q. F. Soper, W. E. Buting, J. E. Cochran, and A. Pohland, *J. Amer. Chem. Soc.*, **76**, 4109 (1954); A. Schönberg, E. Petersen, and H. Kaltschmitt, *Ber.*, **66B**, 233 (1933).

(9) L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 2938 (1950).

(10) Preliminary communication: E. L. Eliel, T. W. Doyle, R. A. Daignault, and B. C. Newman, *J. Amer. Chem. Soc.*, **88**, 1828 (1966).

(11) E. D. Brown, S. M. Iqbal, and L. N. Owen, *J. Chem. Soc., C*, 415 (1966).

(12) A. R. Pinder and H. Smith, *ibid.*, 113 (1954).

(13) E. J. Salmi, *Ber.*, **71B**, 1803 (1938).

(14) R. O. Clinton, C. M. Suter, S. C. Laskowski, M. Jackman, and W. Huber, *J. Amer. Chem. Soc.*, **67**, 594 (1945).

(15) E. L. Eliel, E. W. Della, and M. Rogić, *J. Org. Chem.*, **30**, 855 (1965).

(16) M. P. Mertes, *ibid.*, **28**, 2320 (1963); M. P. Mertes, H. K. Lee, and R. L. Schowen, *ibid.*, **34**, 2080 (1969).

(17) D. J. Pasto, F. M. Klein, and T. W. Doyle, *J. Amer. Chem. Soc.*, **89**, 4368 (1967).

(18) M. F. Shostakovsky, E. N. Prilezhaeva, and E. S. Shapiro, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 325 (1953); 235, 245 (1954).

TABLE I

REDUCTION OF 1,3-OXATHIOLANES WITH CALCIUM IN AMMONIA

Starting material, ethylene monothioketal or monothioacetal of	Product, R′RCHOCH₂CH₂SH R′	R	Registry no.	Yield, %[a] Anal	Isold	Bp, °C (mm)	$n^{25}D$	Carbon, % Calcd	Found	Hydrogen, % Calcd	Found
Acetaldehyde[b]	CH_3	H		9	...[c]						
Isobutyraldehyde[d]	$(CH_3)_2CH$	H		21	7	51–53 (11)	1.4482		...[e]		
Trimethylacetaldehyde	$(CH_3)_3C$	H	24699-65-8	40	22	75 (34)	1.4401	56.73	57.03	10.88	10.85
Benzaldehyde[f]	C_6H_5	H		0	0[g]						
n-Heptanal[f]	*n*-C_6H_{13}	H	24699-66-9	24	3	61 (0.5)	1.4550	61.33	61.53	11.44	11.50
Phenylacetaldehyde	$C_6H_5CH_2$	H	10160-69-7	76	73	100–101 (1.3)	1.5363	65.92	66.00	7.74	7.62
Acetone[f]	CH_3	CH_3		24	16	63–67 (43)	1.4460		...[h]		
3-Methyl-2-butanone	$(CH_3)_2CH$	CH_3	10160-71-1	78	72	63.5–63.8 (11)	1.4470	56.73	56.37	10.88	10.91
4-Methyl-2-pentanone	$(CH_3)_2CHCH_2$	CH_3	10160-72-2	62	54	79 (15)	1.4465	59.23	59.19	11.18	11.06
Pinacolone	$(CH_3)_3C$	CH_3	10160-73-3	90	82	70–71.5 (11)	1.4472	59.23	59.26	11.18	11.05
2,4-Dimethyl-3-pentanone	$(CH_3)_2CH$	$(CH_3)_2CH$	10160-75-5	76	69	57–58.2 (2.2)	1.4532	61.33	61.26	11.44	11.42
Acetophenone[f]	C_6H_5	CH_3		0	0[i]						
2-Octanone[f]	*n*-C_6H_{13}	CH_3	10160-74-4	55	41	62 (0.3)	1.4534	63.12	63.38	11.65	11.56
Phenylacetone	$C_6H_5CH_2$	CH_3	10160-76-6	91	88	97 (0.9)	1.5239	67.32	67.63	8.22	7.80
4-Phenyl-2-butanone	$C_6H_5CH_2CH_2$	CH_3	10160-77-7	59	47	108.5–109.5 (0.9)	1.5228	68.55	68.82	8.63	8.52
Cyclopentanone	$-CH_2CH_2CH_2CH_2-$		10160-78-8	37	25	54 (2.2)	1.4856[j]	57.51	57.61	9.65	9.61
Cyclohexanone[f]	$-CH_2CH_2CH_2CH_2CH_2-$			68	49	84–86 (5)	1.4860		...[k]		
3,3,5-Trimethylcyclohexanone[l]	3,3,5-Trimethylcyclohexyl β-mercaptoethyl ether[m]		24691-50-7	80[n]	61	78–78.5 (0.8)	1.4772	65.31	65.56	10.96	10.87
3,3,5-Trimethylcyclohexanone[l]	3,3,5-Trimethylcyclohexyl β-mercaptoethyl ether			92[o]	...[c]						
4-*t*-Butylcyclohexanone[f]	4-*t*-Butylcyclohexyl β-mercaptoethyl ether[p]		24691-51-8	86[n]	80	100–102 (0.98)	1.4892	66.60	66.66	11.18	11.24
4-*t*-Butylcyclohexanone[f]	4-*t*-Butylcyclohexyl β-mercaptoethyl ether			61[o]	...[c]						

[a] First column gives analytical yields determined by iodine titration. Second column gives yield of compound isolated. [b] K. K. Georgieff and A. Dupré, *Can. J. Chem.*, **37**, 1104 (1959). [c] No attempt made to isolate ompound. [d] F. Kipnis and J. Ornfelt, *J. Amer. Chem. Soc.*, **71**, 3555 (1949). [e] Lit.[18] bp 45.2–45.5° (9 mm), $n^{20}D$ 1.4444. [f] Reference 2a. [g] Toluene obtained in 75% yield. [h] Lit.[18] bp 56.1–56.4° (44 mm), $n^{20}D$ 1.4424. [i] Ethylbenzene obtained in 75% yield. [j] At 22°. [k] Lit.[18] bp 73–73.5° (4.5 mm), $n^{20}D$ 1.4864. [l] Reference 16. [m] Stereochemistry *cis*. [n] From S-axial isomer. [o] From O-axial isomer. [p] Stereochemistry *trans*.

TABLE II

REDUCTION OF 1,3-OXATHIOLANES WITH SODIUM IN AMMONIA

Starting material, ethylene monothioketal of	Product, R'RCHOCH$_2$CH$_2$SH R'	R	Yield, %[a] Anal	Isold
2,4-Dimethyl-3-pentanone	$(CH_3)_2CH$	$(CH_3)_2CH$	62	51
2-Octanone[b]	n-C_6H_3	CH_3	49	41
Cyclopentanone	$-CH_2CH_2CE_2CH_2CH_2-$		25	17
Cyclohexanone[b]	$-CH_2CH_2CH_2CH_2CH_2CH_2-$		55	43
3,3,5-Trimethylcyclohexanone[c]	3,3,5-Trimethylcyclohexyl β-mercaptoethyl ether[f]		64[d]	36
4-t-Butylcyclohexanone[b]	4-t-Butylcyclohexyl β-mercaptoethyl ether[g]		82[d]	70
4-t-Butylcyclohexanone[b]	4-t-Butylcyclohexyl β-mercaptoethyl ether[g]		44[e]	35

[a] First column gives analytical yields determined by iodine titration. Second column gives yield of compound isolated. [b] Reference 2a. [c] Reference 16. [d] From S-axial isomer. [e] From O-axial isomer. [f] *cis* isomer. [g] *trans* isomer.

TABLE III

REDUCTION OF 1,3-OXATHIANES WITH CALCIUM IN AMMONIA

Starting materials, trimethylene monothioacetal or monothioketal of	Product, R'RCHOCH$_2$CH$_2$CH$_2$SH R'	R	Registry no.	Yield, %[a] Anal	Isold	Bp$_1$, °C (mm)	n^{20}D	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
Isobutyraldehyde	$(CH_3)_2CH$	H	24699-76-1	69	66	78 (21)	1.4505	56.73	56.90	10.88	11.18
Pinacolone	$(CH_3)_3C$	CH_3	24699-77-2	96	89	60 (2.7)	1.4505	61.33	61.12	11.44	11.18
Cyclopentanone	$-CH_2CH_2CH_2CH_2-$		24699-78-3	98	85	98–99 (14)	1.4833	59.98	60.21	10.07	10.14
Cyclohexanone[b]	$-CH_2CH_2CH_2CH_2CH_2-$		24699-79-4	90	70	72.5 (0.85)	1.4869	62.04	62.10	10.41	10.34
4-t-Butylcyclohexanone[c]	4-t-Butylcyclohexyl-O(CH$_2$)$_3$SH			84–90[d]	...[f]						
4-t-Butylcyclohexanone[c]	4-t-Butylcyclohexyl-O(CH$_2$)$_3$SH			24–52[e]	...[f]						
4-t-Butylcyclohexanone[c]	4-t-Butylcyclohexyl-O(CH$_2$)$_3$SH		24699-80-7	78[g]	61	98–100 (0.3)	1.4859	67.77	67.80	11.37	11.33

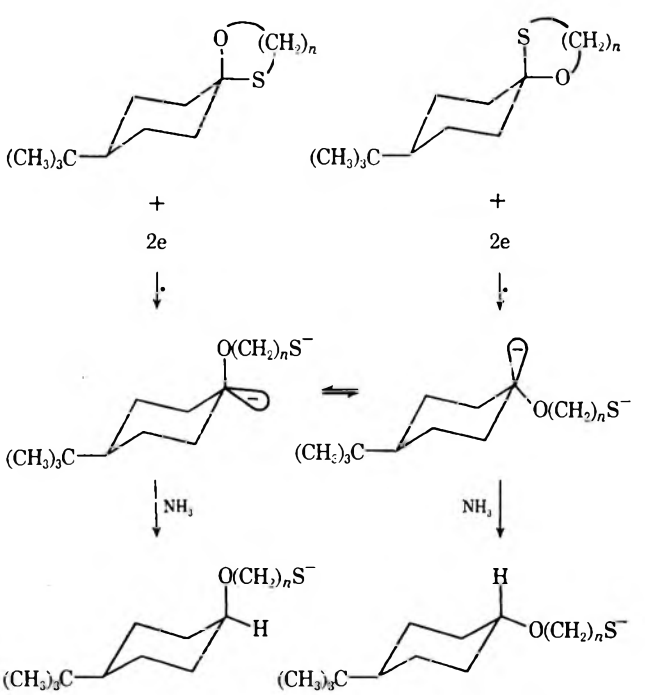
[a] First column gives analytical yields determined by iodine titration. Second column gives yield of compounds isolated. [b] Reference 2a. [c] Reference 15. [d] From S-axial isomer. [e] From O-axial isomer. [f] Compound not isolated. [g] From synthetic mixture (55% O-axial isomer, 45% S-axial isomer) using sodium as the metal.

substituents are cleaved completely to the corresponding alkylbenzenes. The reduction of allyl and benzyl ethers with metal–ammonia solutions has long been known in the literature,[19] thus any β-mercaptoethyl benzyl ethers, $C_6H_5CHROCH_2CH_2S^-$, initially produced by the reduction might well be expected to be cleaved further to the hydrocarbon and β-mercaptoethanol.

While the reduction of monosubstituted 1,3-oxathiolanes generally leads to poor yields of mercaptan, 2-benzyl-1,3-oxathiolane is an exception. Similarly, 2-benzyl-2-methyl-1,3-oxathiolane gives mercaptan in better yield than might be expected on purely steric grounds. This may be ascribed to an inductive electron withdrawal by the benzyl group which enhances the electron affinity of the oxathiolane and thus facilitates its reduction.

Stereochemistry and Reaction Mechanism.—The reduction of oxathiolanes and oxathianes presumably proceeds by the transfer of two electrons, probably stagewise, and addition of a proton from ammonia at the carbon[20] (*cf.* Scheme I). There may be an intermediate radical anion with the anionic center either at the sulfur or at the carbon, and protonation of this anion radical may precede transfer of the second electron.[20] In this connection it is of interest that reduction of the diastereoisomeric oxathiolanes and oxathianes derived from 4-t-butylcyclohexanone[15] is strongly though not completely stereoconvergent (Table IV) with the more stable equatorial β- or γ-hydroxyethyl sulfide being by far the predominant product, regardless of the configuration of the starting material. This suggests that the rate of interconversion of the intermediate dianions or anion radicals (Scheme I) is somewhat more rapid than protonation;

SCHEME I



* This reaction probably proceeds *via* $R_2C^-O(CH_2)_nS\cdot$ or $R_2CO(CH_2)_nS^-$. Protonation (and interconversion of stereoisomers) may, alternatively, occur at the radical-anion stage.

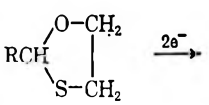
(19) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, New York, 1963, p 151–285.

(20) *E.g.*, R. Gerdil and E. A. C. Lucken, *J. Chem. Soc.*, 2857, 5444 (1963); 3916 (1964), and references there cited.

however, the fact that stereoconvergence is not complete, *i.e.*, that a slightly larger proportion of equatorial (*trans*) ether is obtained from the S-axial monothioketals than from the S-equatorial ones (Table IV) shows that the rates of equilibration and protonation must be of similar magnitude. It is also noteworthy (Table IV) that product yields are consistently lower when the starting material is O axial, which suggests that development of the initially axial carbanion (dicarbanion or anion radical) is less facile than formation of the initially equatorial ion. Predominant formation of the equatorial products from the largely equilibrated carbanion intermediates is in keeping with what is observed in other reactions involving six-membered rings;[21–23] the reasons are probably kinetic (*i.e.*, dependent on rate of proton approach) rather than thermodynamic.[23]

The configuration of the starting materials I–IV had been previously assigned[15] and rests on firm grounds (nmr data, oxidation rates) for I and II and on somewhat less firm ones (nmr data only) for III and IV. Similarly the stereochemistry of the products V and VI was unequivocally established by Raney nickel hydrogenolysis to the known[24] *cis*- and *trans*-4-*t*-butylcyclohexyl ethyl ethers, whereas the assignment for VII and VIII rests on analogy only.

The low yield of β-alkoxy mercaptans from aldehydes and the less branched ketones (Table I) was found to be due, at least in part, to a side reaction leading to alcohol, hydrogen sulfide, and ethylene. Formation of alcohol (and sometimes also a small amount of ketone) was evident from the infrared spectrum. The side reaction was studied in some detail for the ethylene monothioacetal derived from heptaldehyde; *n*-heptyl alcohol (identified by boiling point, refractive index, and infrared spectrum), ethylene (identified mass spectrometrically as constituting 90+% of the off-gas), and hydrogen sulfide (identified by odor and by formation of lead sufide) were found to be present. A reasonable reaction course is shown in eq 2. The



$$S^{2-} + CH_2{=}CH_2 + RCHO \xrightarrow[NH_3]{2e^-} RCH_2O^- \quad (2)$$

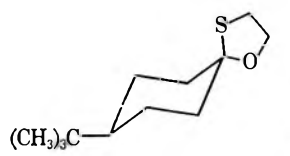
alcohol product presumably results from further reduction of aldehyde; it was shown independently that a carbonyl compound (4-*t*-butylcyclohexanone) is reduced under the conditions of the reaction (see ref 23). The products shown in eq 2 are derived directly from the monothioacetal rather than from the alkoxy mercaptan, $RCH_2OCH_2CH_2SH$, formed from it, for β-cyclohexyloxyethyl mercaptan was unaffected by sodium in liquid ammonia. Our proposed mechanism for the side reaction as well as the mercaptan forming reaction is shown in Scheme II.

Although attack of organolithium compounds both at the 2 position[25,26] and at the 4 position[27] of dioxolanes, leading to cleavage of the ring, has been reported, it was found that 2-*n*-hexyloxathiolane is unaffected by calcium amide; thus the cleavage reaction in our case must be associated with reduction and cannot be due just to the presence of base.

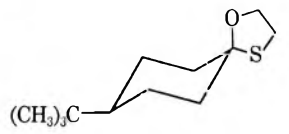
While we do not have a complete understanding of the counterplay of reduction and cleavage mech-

TABLE IV

STEREOCHEMISTRY OF REDUCTION OF 1-OXA-4-THIA-8-*t*-BUTYLSPIRO[4.5]DECANES (I, II) AND 1-OXA-4-THIA-9-*t*-BUTYLSPIRO[5.5]UNDECANES (III, IV) WITH CALCIUM OR SODIUM IN LIQUID AMMONIA



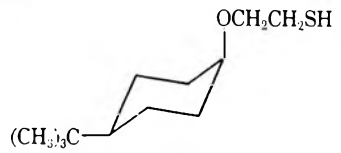
I



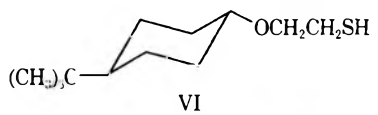
II

III

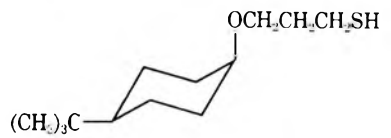
IV



V



VI



VII

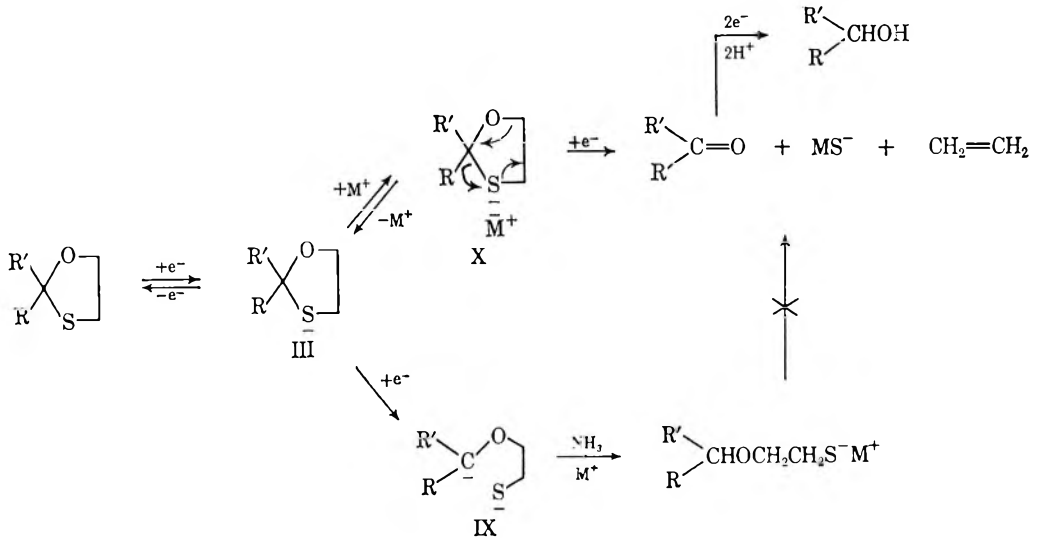
VIII

Substrate used	Yield, % $RO(CH_2)_nSH$	Metal used	Isomer distribution[a] % *cis* (V or VII)	Isomer distribution[a] % *trans* (VI or VIII)
I[b]	83–89	Ca	1.9–3.0	97.0–98.1
I	75–82	Na	2.5	97.5
II[c]	47–61	Ca	3.5–10.4	89.6–96.5
II[d]	44–46	Na	3.8–4.8	95.2–96.2
III[e]	84–90	Ca	0.5	99.5
IV[e]	24–52	Ca	6.8–15.6	84.4–93.2
III, IV[f]	80	Ca	6.5	93.5

[a] By gas chromatography of the products or, in the case of I and II, the ethyl ethers derived from V and VI by desulfurization. [b] Average of six runs. [c] Average of five runs. [d] Average of two runs. [e] Average of three runs. [f] 1:1 mixture.

(21) E. L. Eliel and Y. Senda, *Tetrahedron*, in press.
(22) J. C. Richer, *J. Org. Chem.*, **30**, 324 (1965).
(23) *Cf.* J. W. Huffmann and J. T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968); D. A. H. Taylor, *Chem. Commun.*, 476 (1969).
(24) E. L. Eliel and S. Krishnamurthy, *J. Org. Chem.*, **30**, 848 (1965).
(25) P. S. Wharton, G. A. Hiegel, and S. Ramaswami, *ibid.*, **29**, 2441 (1964); K. D. Berlin, B. S. Rathore, and M. Peterson, *ibid.*, **30**, 226 (1965); T. L. V. Ulbricht, *J. Chem. Soc.*, 6649 (1965).
(26) 1,3-Oxathiolanes are also reported to undergo such a reaction: personal communication from D. Seebach.
(27) C. H. Heathcock, J. E. Ellis, and R. A. Badger, *J. Heterocycl. Chem.*, **6**, 139 (1969).

SCHEME II



anisms (Scheme II), the following additional findings are of interest.

(1) The effectiveness of metals in reduction is Ca > Li > Na > K. The consistently lesser yields obtained by sodium compared with calcium are seen by comparison of Table II with Table I; more extensive studies with cyclohexanone ethylene monothioketal showed a drop in analytical yield from 69 ± 3% (Ca) to 62 ± 1% (Li) to 48 ± 7% (Na) to 38 ± 2% (K). Addition of $CaCl_2$ in reduction with Na does not effect the yield, but addition of KBr in reduction with Ca lowers the yield by about 25%.

(2) Optimum concentration of metal is about 0.35 *N*. Increase to 0.70 *N* with Ca had little effect on mercaptan yield but increasing [Na] above 1 *N* or below 0.1 *N* led to a 10–15% drop.

(3) The addition of proton–donor (*t*-BuOH, EtOH) cosolvents is not helpful; if anything, it tends to lower the yield slightly. Added ether lowers the yield considerably.

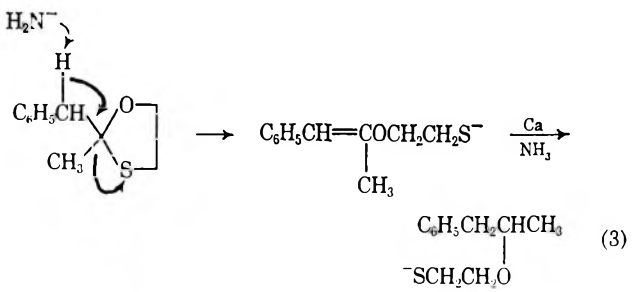
(4) Use of $MeNH_2$ and $EtNH_2$ with Li gave lower yields than NH_3.

(5) The yields are much better for oxathianes (which cannot undergo the cleavage shown in eq 2) than for oxathiolanes, suggesting that the cleavage is responsible for the low yield of mercaptans in some of the cases shown in Table I.

(6) More branched structures (Table I, bottom half) give better yields of mercaptan than less branched ones (Table I, top entries).

We tentatively suggest that formation of a radical ion pair (X, Scheme II) is responsible for the competing cleavage reaction. It would appear[28,29] that the ease of ion-pair formation is $K^+ > Na^+ > Li^+$ which explains why K favors cleavage most. Lowering the dielectric constant of the solvent (NH_3–ether *vs.* NH_3 alone, $MeNH_2$, or $EtNH_2$ *vs.* NH_3) favors cleavage, as is required by this explanation; so does the addition of the strongly pairing K^+ in reduction with Ca. Branching may interfere sterically with ion-pair formation, thus favoring reduction over cleavage. An alternative explanation of one-electron transfer, leading to cleavage, *vs.* two-electron transfer, producing reduction,[20] *without* invoking ion-pair formation cannot readily account for the effects of variation in metal, solvent, and substrate structure on mercaptan yields which we have observed.

It was earlier noted that oxathiolanes with a 2-benzyl substituent give an unusually high yield of reduction product (Table I), and this was ascribed to the inductive effect of the phenyl group. An alternative explanation, namely that an abstraction of the benzylic hydrogen by base, followed by formation of an enol ether and subsequent reduction of that ether (eq 3), might be involved, could be ruled out on two



(3)

counts. First of all, β-ethoxystyrene, PhCH=CHOEt, chosen as a model for the proposed intermediate enol ether, was found to yield ethylbenzene rather than β-phenethyl ethyl ether, $PhCH_2CH_2OEt$, when treated with calcium in liquid ammonia (even though the latter ether is stable to this combination). Secondly, when all the hydrogens on the carbons at C-2 in 2-methyl-2-benzyloxathiolane (eq 3) were replaced by deuterium by preparing the oxathiolane from $PhCD_2$-$CCOCD_3$ and reduction was carried out, the product, $PhCD_2CH(CD_3)OCH_2CH_2SH$, had acquired no hydrogen at the benzyl (or methyl) position, as shown by nmr spectroscopy. Equation 3 would require replacement of one of the benzylic deuterium atoms by hydrogen in the reduction.

Several new compounds prepared in conjunction with this study but not heretofore mentioned are listed at the end of the Experimental Section.

(28) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 318 (1966). We could find no data on Ca.

(29) See also T. S. Das, *Advan. Chem. Phys.*, **4**, 303 (1962).

TABLE V

STARTING MATERIALS[a]

Ethylene ketal or monothioacetal of	Registry no.	Yield, %	Bp, °C (mm)	$n^{20}D$	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
Isobutyraldehyde[b]	17643-70-8	79	166–168 (745)	1.4783				
Trimethylacetaldehyde	17643-69-5	83	59.5 (13)	1.4754	57.51	57.66	9.65	10.00
Phenylacetaldehyde	24699-49-8	74	111 (1.5)	1.5705	66.65	66.84	6.71	6.63
3-Methyl-2-butanone	16047-98-6	73	64–65 (11)	1.4783	67.61	67.80	9.65	9.65
4-Methyl-2-pentanone	21-87-9	73	51–51.5 (3)	1.4740	59.98	60.11	10.07	10.11
Pinacolone	17642-77-2	75	75–77 (15)	...[c]	59.98	60.13	10.07	9.69
2,4-Dimethyl-3-pentanone	16047-99-7	50	57.1–57.5 (1.9)	1.4822[d]	62.02	61.88	10.41	10.41
Cyclopentanone	176-38-5	89	29.5 (0.2)	1.5097[e]	58.31	58.52	8.39	8.43
3,3,5-Trimethylcyclohexanone	24699-55-6	70	64–70 (0.3)	...[f]	...[g]			
Phenylacetone	17642-77-2	72	94 (0.7)	1.5590	68.02	68.12	7.27	6.98
1-Phenylpentadeuteriopropanone[h]	24699-57-8	87	83–85 (0.2)	1.5572				
4-Phenyl-2-butanone	17642-78-3	85	100–102 (0.45)	1.5480	69.21	69.43	7.74	7.93
Trimethylene acetal or monothioketal of								
Isobutyraldehyde	24699-59-0	49	74–75 (13)	1.4871	57.51	57.74	9.65	9.65
Pinacolone	24699-60-3	20	49–49.5 (0.5)	1.4935	62.04	62.30	10.41	10.71
Cyclopentanone	24699-61-4	54	81.5–82.6 (4)	1.5205	60.74	60.54	8.72	8.73

[a] Materials earlier prepared in this laboratory (ref 2a, 15) are not listed. [b] F. Kipnis and J. Ornfelt, *J. Amer. Chem. Soc.*, 71, 3555 (1949), report bp 29° (2.5 mm). The nmr spectrum confirmed the assigned structure. [c] Solidifies to a glass, softening point 40–42°. [d] $n^{22}D$. [e] $n^{25}D$. [f] Separated, by column chromatography on Alcoa F-20 alumina, into an isomer of bp 60–61° (0.25 mm), $n^{20}D$ 1.4992, and one of bp 84° (10.9 mm), $n^{20}D$ 1.5004. Nmr spectra were compatible with the assigned structures. [g] Reference 16 reports bp 118–131° (19 mm); both isomers are described. [h] The nmr spectrum of the oxathiolane was identical with that of the derivative from phenylacetone except for the near absence of the methyl and benzyl (CH_2) resonances at 1.45 and 2.98 ppm (downfield from TMS). Extent of deuteration as estimated from nmr spectrum: 90% at CD_2, 92% at CD_3.

Experimental Section

All boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer infracord instrument. Gas chromatograms were obtained on a F & M Scientific Co. Model 810 research chromatograph. Nuclear magnetic resonance spectra were recorded with a Varian Associates Model V-4311 HR-60 spectrometer at 60 Mc by Mr. D. Schifferl. Complete ir and nmr spectra are recorded in the Ph.D. Thesis of T. W. Doyle (1966) available on interlibrary loan from the University of Notre Dame library. Elemental analyses were performed by either Midwest Microlab, Indianapolis, Ind., or Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Starting Materials.—The preparation of the starting materials used in this investigation was carried out according to the method of Eliel, Pilato, and Badding.[2a] The properties of all new starting materials are listed in Table V. Known starting materials agreed in their physical properties with samples previously prepared and described in the literature.

Reductions.—The reduction of phenylacetone ethylene monothioketal has been described previously in detail.[10] Other oxathiolane reductions were effected similarly. Yields and properties of reduction products are listed in Tables I and II. Analytical yields of mercaptan were determined by iodine titration.[30]

Reduction of the Ethylene Monothioketal of 1-Phenylpentadeuteriopropanone with Calcium in Ammonia.—The reduction of the ethylene monothioketal of 1-phenylpentadeuteriopropanone (3.88 g, 0.02 mol) with calcium (1 g, 0.025 g-atom) in liquid ammonia (250 ml) was carried out in the usual fashion. The usual work-up procedure gave 3.86 g of an oil. A small aliquot of this oil was removed and titrated for mercaptan content with iodine[30]; the yield of mercaptan was 98%. The remaining oil (3.30 g) was distilled to yield 3.24 g (94%) of the desired mercaptan, bp 82° (0.2 mm), $n^{20}D$ 1.5250. The nmr spectrum of the compound showed 1.27 H (compared with 4 in the indeuterated compound) at 0.84–1.52 ppm and 2.18 H (compared with 4) at 2.23–2.90 ppm. If three of the four high-field hydrogens of the undeuterated compound are assigned to the CH_3 group and two of the four low-field ones to the $PhCH_2$ group, this indicates labeling in the benzylic position to be 91% complete and deuterium labeling in the methyl position to be 91% complete (which is approximately the amount of labeling in the starting material).

(30) D. P. Harnish and D. S. Tarbell, *Anal. Chem.*, **21**, 968 (1949).

Reduction of 2-*t*-Butyl-2-methyl-1,3-oxathiane.—The reduction of 2-*t*-butyl-2-methyl-1,3-oxathiane is described in some detail. Other reductions of oxathianes were effected similarly. Yields and properties of reduction products are listed in Table III.

To 120 ml of liquid ammonia contained in a 300-ml, three-necked flask, fitted in the usual manner, was added 1 g (0.025 g-atom) of calcium turnings. When the metal had dissolved (after *ca.* 5 min) a solution of 2.08 g (0.012 mol) of 2-*t*-butyl-2-methyl-1,3-oxathiane in 12 ml of ether was added dropwise to the blue solution over a period of 2 min. When addition was complete the blue solution was stirred for 1 hr. At the end of this time the excess calcium was decomposed by the addition of small amounts of solid ammonium chloride. The reaction mixture was then worked up in the usual manner to yield 2.15 g of an oil. A small aliquot of this oil was removed and titrated for mercaptan content with iodine;[30] the yield of mercaptan was 96%. The remaining oil (1.95 g) was distilled to yield 1.70 g (89%) of γ-mercaptopropyl 3,3-dimethyl-2-butyl ether, bp 60° (2.7 mm) (see Table III). The infrared and nmr spectra were compatible with the assigned structure.

Stereochemistry.—The reductions of the diastereoisomeric 1,3-oxathiolane and 1,3-oxathianes derived from 4-*t*-butylcyclohexanone were carried out in the usual manner. After work-up the per cent yield of mercaptan was determined iodometrically for each reaction. The isomer composition of the products was determined by glpc analysis.

In the case of the products from the reduction of the diastereoisomeric 1,3-oxathiolanes the analysis was either carried out directly on the β-mercaptoethyl 4-*t*-butylcyclohexyl ethers or the mercaptans were first desulfurized with Raney nickel (see below) to give the corresponding ethyl ethers which were then analyzed by glpc. The mercaptans were analyzed on a 9-ft 20% Carbowax 20M on 42–60 firebrick column at 200° and a flow rate of 75 ml/min. The ethers were analyzed on the same column at 150°. The products from the reduction of the diastereoisomeric 1,3-oxathianes were analyzed directly by glpc on a 9-ft 20% Carbowax 20M on 42–60 firebrick column at 215° and a flow rate of 75 ml/min. The results of these experiments are summarized in Table IV.

Raney Nickel Desulfurization of β-Mercaptoethyl 4-*t*-Butylcyclohexyl Ether.—Raney nickel (5 g, W-2 grade commercial) was washed once with acetone, once with ethanol, and three times with ether (very carefully!). The 0.5 g of the oil recovered from the metal–ammonia reduction of the oxathiolane was dissolved in 25 ml of ether and added to the nickel. The mixture

was refluxed for 20 min, cooled, and decanted from the nickel which was washed with three 10-ml portions of ether. The combined ethereal extracts were dried over magnesium sulfate and concentrated. The oil was then taken up in 2 ml of hexane and chromatographed on alumina (5–10 g, Alcoa F-20) with hexane to remove alcohol and ketone (produced in the metal–ammonia reduction). The eluent was concentrated and analyzed by glpc on a 9-ft 20% Carbowax 20M on firebrick column at 150°.

cis-**3,3,5-Trimethylcyclohexyl Ethyl Ether.**—*cis*-3,3,5-Trimethylcyclohexanol[31] (20 g) was converted to its acetate by treatment with acetic anhydride (50 ml) and pyridine (10 g) (4 hr heating on steam bath). The acetate (23 g, 89%) boiled at 72° (3.5 mm), n^{20}D 1.4392.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 72.07; H, 11.19.

Reduction was carried out by the method of Pettit and coworkers[32] starting with 4.92 g of the acetate in 120 ml of boron trifluoride etherate which was added to 2.28 g of $LiAlH_4$ in 60 ml of ether. Reaction was effected with cooling for 90 min followed by 1-hr reflux. After decomposition with 10% sodium hydroxide the ether layer was concentrated, chromatographed over Alcoa F-20 alumina with hexane and concentrated again to give upon distillation 2.5 g (55%) of *cis*-3,3,5-trimethylcyclohexyl ethyl ether, bp 77–80° (20 mm). Repetition of the chromatography yielded pure material, bp 48–49° (3.5 mm), n^{20}D 1.4350.

Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.64; H, 13.05.

trans-**3,3,5-Trimethylcyclohexyl ethyl ether** was synthesized analogously from the *trans* alcohol.[31] The acetate, bp 60–60.5° (2 mm), n^{20}D 1.4399, was obtained in 82% yield.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 72.04; H, 11.15.

The ether was obtained in 68% yield, bp 74–75° (20 mm), n^{20}D 1.4338.

Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.86; H, 13.40.

trans-**4-*t*-Butylcyclohexyl propyl ether** was obtained analogously from *trans*-4-*t*-butylcyclohexanol and propionic anhydride, followed by reduction. The ether boiled at 112–114° (10 mm), n^{20}D 1.4476.

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 79.13; H, 13.20.

trans,trans-**4-*t*-Butylcyclohexyloxyethyl Disulfide.**—*trans*-4-*t*-Butylcyclohexyloxyethyl mercaptan of 98% stereoisomeric purity (Table IV) (0.95 g, 4.5 mmol) in 8 ml of 5% NaOH solution was treated with 0.5 ml of 30% hydrogen peroxide. Excess peroxide was destroyed with solid sodium metabisulfite and the product was extracted three times with a 20-ml portion of ether. Drying and concentration yielded 0.92 g (97%) white solid, recrystallized from ethanol to give white plates, mp 51.5–52°.

Anal. Calcd for $C_{24}H_{46}O_2S_2$: C, 66.92; H, 10.77; S, 14.89. Found: C, 67.16; H, 10.76; S, 14.77.

β-Chloroethyl benzyl sulfide was prepared from 40 g (0.25 mol) of β-hydroxyethyl benzyl sulfide[2a] and 120 ml of concentrated hydrochloric acid by refluxing (with a gas trap) for 4 hr. The mixture was poured into 200 ml of water, the organic layer separated, and the aqueous layer was twice extracted with 100-ml portions of ether. The combined organic product was washed once with water and once with concentrated aqueous NaCl, dried, and concentrated to give after distillation 33 g (75%) of β-chloroethyl benzyl sulfide, bp 91.5° (0.6 mm), n^{20}D 1.5682.

Anal. Calcd for $C_9H_{11}ClS$: C, 57.89; H, 5.93; Cl, 18.99. Found: C, 58.44; H, 6.00; Cl, 18.86.

Registry No.—*cis*-3,3,5-Trimethylcyclohexyl ethyl ether, 24691-15-4; *cis*-3,3,5-trimethylcyclohexanol (acetate), 24691-16-5; *trans*-3,3,5-trimethylcyclohexyl ethyl ether, 24691-17-6; *trans*-3,3,5-trimethylcyclohexanol (acetate), 24691-18-7; *trans*-4-*t*-butylcyclohexyl propyl ether, 24691-19-8; *trans,trans*-4-*t*-butylcyclohexyloxyethyl disulfide, 24691-20-1; β-chloroethyl benzyl sulfide, 4332-51-8.

(31) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).

(32) G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and I. M. Piatak, *ibid.*, **26**, 1685 (1961).

Aromatic Nitration by Silver Nitrate Impregnated Silicic Acid in the Presence of Carbon Tetrachloride

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Carbon tetrachloride reacts rapidly with excess silver nitrate impregnated silicic acid at room temperature to produce carbon dioxide and a nitrating agent. With carbon tetrachloride in excess, phosgene and the nitrating agent are formed. Aromatic compounds are nitrated by this system under column-chromatographic or batch conditions. A reaction sequence involving trichloromethyl nitrate, phosgene, nitryl chloride, carbonyl nitrate, and dinitrogen pentoxide is proposed.

While chromatographing *trans*-stilbene on $AgNO_3$–silicic acid, we attempted to elute with carbon tetrachloride. The result was complete destruction of the stilbene with formation of some 4,4′-dinitrostilbene.[1] We have observed nitration of several other aromatic compounds under these conditions, but none of these reactions occurs in the absence of carbon tetrachloride.[1,2] Carbon tetrachloride is generally considered inert to silver nitrate in homogeneous solution.[3] Petrenko-Kritschenko and Opotsky[4] reported 3% reaction with 0.2 *N* silver nitrate in 95% ethanol at 90° in 12 hr; the products were not examined. We were thus interested to attempt identification of the reactions involved.

Results

Static batch experiments with benzene and anisole are summarized in Table I. The basic experimental results drawn from there and the Experimental Section follow. (1) Neither benzene nor anisole is nitrated by $AgNO_3$–silicic acid alone (expt 8, 18). Both are nitrated in high yield by $AgNO_3$–silicic acid in the presence of CCl_4 (expt 16, 17). (2) The nitration reaction involves specifically Ag^+, NO_3^-, CCl_4, and the silicic acid surface (expt 6, 8, 9; ref 4). (3) The nitration reaction is independent of illumination and the presence of air (expt 3, 4, 11, 12). (4) Phosgene is formed in quantity. Two independent determinations

(1) J. E. Gordon, *J. Chromatogr.*, **48**, 532 (1970).

(2) E. Wenkert, D. J. Watts, and L. L. Davis [*Chem. Commun.*, 1317 (1969)], have recently reported nitration of phenols by $AgNO_3$–silicic acid alone. This appears to depend upon the presence of the acidic OH group.

(3) See, *e.g.*, R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 136 ff.

(4) P. Petrenko-Kritschenko and V. Opotsky, *Ber.*, **59**, 2131 (1926).

TABLE I

NITRATION OF BENZENE AND ANISOLE

Expt	C_6H_6, mmol	$C_6H_5OCH_3$, mmol	CCl_4, mmol	$AgNO_3$, mmol	Solvent[a]	Other conditions	Reaction time, hr: CCl_4 + $AgNO_3$	Reaction time, hr: CCl_4 + $AgNO_3$ + ArH	Limiting[b] reagent	Yield, mmol of $ArNO_2$/mmol of limiting reagent
1	2.74		c	4.26	CCl_4		2.8	2.8	$AgNO_3$	0.042
2	2.74		c	4.70[d]	CCl_4–C_6H_{14}		2.8	2.8	$AgNO_3$	0.060 ± 0.005[d]
3	2.74		c	4.6	CCl_4–C_6H_{14}	Bubbled N_2	2.8	2.8	$AgNO_3$	0.14
4	2.74		c	4.6	CCl_4–C_6H_{14}	Bubbled air	2.8	2.8	$AgNO_3$	0.14
5	220		c	4.39	CCl_4–C_6H_6		3.5	3.5	$AgNO_3$	0.0
6	2.74		0	4.72	$CHCl_3$		11	11	$AgNO_3$	0.0
7	2.74		c	4.71	CCl_4–$CHCl_3$		22	22	$AgNO_3$	0.0
8	c		0	4.49	C_6H_6			24	$AgNO_3$	0.0
9	2.74		c	5.92	CCl_4–C_6H_{14}	$NaNO_3$, not $AgNO_3$	24	24	$AgNO_3$	0.0
10	2.74		c	4.70[e]	CCl_4–C_6H_{14}		24	24	$AgNO_3$	0.41 ± 0.02[e]
11	2.74		c	4.79	CCl_4–C_6H_{14}		48	48	$AgNO_3$	0.48
12	2.74		c	5.04	CCl_4–C_6H_{14}	Dark	48	48	$AgNO_3$	0.51
13	2.74		c	2.63	CCl_4–C_6H_{14}		91	91	$AgNO_3$	0.51
14	2.74		c	4.02	CCl_4–C_6H_{14}		97	97	$AgNO_3$	0.47
15	2.74		c	5.01	CCl_4–C_6H_{14}		90	90	$AgNO_3$	0.52
16	2.68		c	6.12	CCl_4–C_6H_{14}		144	144	C_6H_6	1.01
17		2.25	c	4.68	CCl_4–C_6H_{14}		21	21	$C_6H_5OCH_3$	0.71[f]
18		2.82	0	5.34	C_6H_{14}		70	70	$AgNO_3$	0.0
19		9.1	0.975	6.49	C_6H_{14}		1.2	58	CCl_4	0.38
20		9.1	0.975	5.86	C_6H_{14}		1.0	18	CCl_4	0.25
21		9.1	0.975	5.83	C_6H_{14}		5.0	18	CCl_4	0.71
22		9.1	0.975	5.92	C_6H_{14}		10	18	CCl_4	0.20
23		9.1	0.975	12.8	C_6H_{14}		5.0	18	CCl_4	1.32[g]

[a] Volume ratios of mixed solvents: CCl_4–C_6H_{14}, 1:2; CCl_4–C_6H_6, 1:1; CCl_4–$CHCl_3$, 1:1. [b] Based on eq 1 or 2. [c] Large excess. [d] Mean of two experiments. [e] Mean of three experiments. [f] Isomer composition: 21% *ortho*, 79% *para*. [g] Isomer composition: 20% *ortho*, 80% *para*.

yielded 0.27 and 0.24 mol $COCl_2$/mol of $AgNO_3$ (CCl_4 in excess). Phosgene production is complete in 2 hr. (5) Dinitrogen tetroxide appears in the $AgNO_3$–silicic acid–CCl_4 reaction mixture after a few hours in the absence, but not in the presence of aromatic substrate. (6) Mass spectrometric observation of the $AgNO_3$–silicic acid–CCl_4 reaction mixture reveals only phosgene, CCl_4, and traces of CO_2 when CCl_4 is in excess, but, when CCl_4 is in deficiency, CO_2 is present in quantity. (7) No chlorobenzene could be detected in the $AgNO_3$–silicic acid–CCl_4–C_6H_6 reaction product. (8) With $AgNO_3$ as the limiting reagent, the $ArNO_2$ yield levels off after 48 hr (room temperature) at a limiting $ArNO_2$:$AgNO_3$ ratio of 0.50 ± 0.02 (expt 2, 10, 11, 13–15). (9) The stoichiometry with respect to CCl_4 could not be accurately determined owing to the slowness of the $AgNO_3$–CCl_4 reaction when CCl_4 is limiting, so that decomposition of the nitrating agent becomes competitive. Also, inhibition of the $AgNO_3$–CCl_4 reaction by ArH (see 12 below) was so severe with CCl_4 in deficiency that reasonable yields could be obtained only by allowing the $AgNO_3$–CCl_4 reaction to proceed for some hours, using a large excess of $AgNO_3$–silicic acid, then adding excess ArH. The $ArNO_2$ yield passes through a maximum as the CCl_4–$AgNO_3$ reaction time increases (expt 20–22), and the maximum $ArNO_2$:CCl_4 ratio observed is 1.32 (expt 23). (10) The nitrating agent cannot be eluted from $AgNO_3$–silicic acid with CCl_4. (11) The *ortho/para* ratio in the nitration of anisole is 0.25 with CCl_4 in excess or deficiency (expt 17, 23). (12) Aromatic substrates inhibit the CCl_4–$AgNO_3$–silicic acid reaction (expt 5, expt 19 *vs.* 21; see Experimental Section.) (13) Substitution of alumina for silicic acid in expt 11 reduces nitrobenzene production from 0.48 to 0.02 mol/mol of $AgNO_3$.

Discussion

We believe that eq 1 and 2 give the simplest description of these reactions which is capable of rationalizing all of the observations. When the observed nitro-

$$CCl_4 + 2AgNO_3 + ArH = 2AgCl + COCl_2 + ArNO_2 + HNO_3 \quad (1)$$

$$CCl_4 + 4AgNO_3 + 2ArH = 4AgCl + 2ArNO_2 + CO_2 + 2HNO_3 \quad (2)$$

benzene production in presence of excess CCl_4 (0.50 ± 0.02 mol/mol of $AgNO_3$) is corrected for the slow nitration of benzene by the nitric acid formed according to eq 1 and 2, the net yield becomes 85–90% of the theoretical yield for these processes. The formation of 0.25 mol $COCl_2$/mol $AgNO_3$ implies parallel occurrence of eq 1 and 2, *i.e.*, competition between CCl_4 and $COCl_2$ for the available $AgNO_3$ such that some $COCl_2$ remains when the $AgNO_3$ is exhausted. When CCl_4 is the limiting reagent, eq 2 should apply alone. The difficulties in establishing the stoichiometry under these conditions have been described. Correcting the maximum $ArNO_2$:CCl_4 ratio observed (1.32) for nitration by the nitric acid formed according to eq 2 gives a net value of 1.0. Since we know that the nitrating agent is decomposing with time and that side-reaction products are formed in the nitration step, the experimental results require a $ArNO_2$:CCl_4 stoichiometry >1:1.

The detailed course of reactions 1 and 2 has not been rigorously established. However, both can be ac-

counted for by individual steps which are in accord with our observations and for which reasonable precedents are available. The sum of eq 3–8 is eq 2; eq 1 is the sum

$$CCl_4 + AgNO_3 \longrightarrow CCl_3ONO_2 + AgCl \quad (3)$$

$$CCl_3ONO_2 \longrightarrow COCl_2 + NO_2Cl \quad (4)$$

$$NO_2Cl + AgNO_3 \longrightarrow N_2O_5 + AgCl \quad (5)$$

$$COCl_2 + 2AgNO_3 \longrightarrow 2AgCl + CO(ONO_2)_2 \quad (6)$$

$$CO(ONO_2)_2 \longrightarrow CO_2 + N_2O_5 \quad (7)$$

$$2ArH + 2N_2O_5 \longrightarrow 2ArNO_2 + 2HNO_3 \quad (8)$$

of eq 3–5 and half of eq 8. The trichloromethyl nitrate of eq 3 is not known, but trichloromethyl perchlorate can be prepared from CCl_4 and solid $AgClO_4$ in the presence of AgCl, and it decomposes to phosgene.[5] Trichloromethanol is unknown; it decomposes to phosgene and HCl.[6] Equation 5 is a known reaction.[7] Acyl chlorides react with $AgNO_3$ to give acyl nitrates in analogy with eq 6.[8] The acyl nitrates undergo facile thermal disproportionation to N_2O_5 and carboxylic anhydride in analogy with eq 7.[8] Dinitrogen pentoxide is known to nitrate benzene instantly in CCl_4 solution at 20°; in nitration by benzoyl nitrate, N_2O_5 is the actual nitrating agent.[9] Dinitrogen pentoxide also decomposes thermally to NO_2–$N_2O_4 + O_2$ in the gas phase and in solution with a half-life of a few hours at room temperature.[10]

Anisole is nitrated by N_2O_5 (or by $2ArCOONO_2 \rightleftarrows (ArCO)_2O + N_2O_5$[9]) predominantly in the *ortho* position, whereas the CCl_4–$AgNO_3$–silicic acid reagent gives the predominance of *para* nitration characteristic of nitronium ion nitrations.[11] However, it has been shown that the second-order nitration by molecular N_2O_5 in CCl_4 is replaced in the presence of HNO_3 by higher order processes catalyzed by HNO_3 and involving solvated nitronium ion as the nitrating agent.[12] There is physical evidence that drying at 120–180° removes all of the adsorbed water from the silicic acid surface,[13] but treatment of such material with dichlorodimethylsilane produces hydrolysis products of $(CH_3)_2SiCl_2$.[14] In view of this and because the dried $AgNO_3$–silicic acid samples used in this work were not handled in a strictly anhydrous atmosphere, it is most likely that some hydrolysis of N_2O_5 occurs; the orientation pattern observed is therefore reasonable.

The origin of the surface catalysis of eq 3 is of some interest. This is very likely catalysis by AgCl. The reaction of CCl_4 with solid $AgClO_4$ requires initiation by a small amount of HCl.[5] Also, it has recently been shown that the familiar reaction 9 proceeds simultaneously by homogeneous and heterogeneous paths; AgI is a good surface catalyst and the reaction is autocatalytic.[15] Inhibition of the CCl_4–$AgNO_3$ reaction by benzene is difficult to account for in homogeneous solution because the formation constant for $C_6H_6 \cdot Ag^-$ is small.[16] However, if Ag^+ adsorbed on an initially small amount of AgCl[17] is the active reagent, this might be susceptible to more complete complexation by C_6H_6. The comparatively poor performance of $AgNO_3$–alumina may stem from a smaller surface area.

$$C_2H_5I + AgNO_3 + H_2O \longrightarrow C_2H_5OH + AgI + HNO_3 \quad (9)$$

We have given elsewhere some examples of nitrations by CCl_4–$AgNO_3$–silicic acid under chromatographic conditions.[1] Should this system ever be used to deliberately nitrate small samples, limitations of solubility in CCl_4 would be encountered with many compounds, since most other solvents except saturated hydrocarbons react with the reagent. We investigated the possibility of nitrating 2,4-dinitrophenol, which is poorly soluble in carbon tetrachloride, by stirring a suspension with CCl_4–$AgNO_3$–silicic acid. This produced a clean reaction mixture and 49% picric acid in 24 hr at room temperature, along with 45% recovered starting material.

Experimental Section

General.—All reactions were conducted at 24 ± 2°. Product analyses, except where otherwise stated, were *via* gas chromatography using silicone QF-1 columns (20% on acid-washed Chromosorb W) in a F & M 700 instrument with a thermal conductivity detector. Peak areas from duplicate 20-μl samples were planimetrically compared with those from standard solutions prepared from Fisher Certified Reagent or Eastman White Label materials and chromatographed before and after the unknown. Linearity of detector response was verified over the concentration range employed. Nitrobenzene was chromatographed at 150°, the nitroanisoles at 200°. The analytical precision was ~1%.

Melting points were determined by hot stage microscopy and are uncorrected. Mass spectra were measured on a GEC-AEI MS-12 instrument. Infrared and electronic spectra were recorded on Perkin-Elmer Model 337 and 202 instruments.

Silver Nitrate Impregnated Silicic Acid and Aluminum Oxide.—Mallinckrodt chromatographic silicic acid (6.1% water loss at 150°), 56.1 g, was slurried with 160 ml of methanol and added to a solution of 14.00 g of silver nitrate in 60 ml of 50% aqueous methanol. The resulting slurry was evaporated at 40–55° and 15 Torr in a rotary evaporator to yield a white powder which was lightly ground in a Pyrex mortar. The product was dried to constant weight at 150° just before use, and the resulting samples thus contained 1.24 mmol of $AgNO_3$/g. Material which was dried to constant weight at 120° possessed the same chemical properties. Impregnated alumina was prepared in the same way, using Merck acid-washed chromatographic alumina and a nominal 15 wt % loading rather than the above 20%; the dried product contained 0.932 mmol of $AgNO_3$/g.

Observations on CCl_4–$AgNO_3$–Silicic Acid Mixtures.—(a) A 50 mg sample of $AgNO_3$–silicic acid was covered with CCl_4; after 1 hr it was frozen, evacuated, and allowed to warm until a vapor pressure of *ca.* 10^{-4} Torr resulted. The vapor was then observed mass spectrometrically, using an exciting potential of 70 eV. After subtracting the lines due to CCl_4, the following peaks remained: *m/e* (relative abundance) 36 (25), 38 (10), 44 (32), 63 (100), 64 (1.2), 65 (36), 98 (9.3), 100 (5.4), 102 (1.1). A similar experiment using CCl_4 adsorbed on an excess of $AgNO_3$–silicic acid gave the following spectrum: 30 (2.6), 35 (4.9), 36 (0.5), 37 (1.4), 38 (0.1), 44 (100), 45 (2.4), 46 (1.1), 63 (18),

(5) L. Birckenbach and J. Goubeau, *Naturwissenschaften*, **18**, 530 (1930); *Ber.*, **64B**, 218 (1931).
(6) K. Elbs and K. Kratz, *J. Prakt. Chem.*, **55** [2], 502 (1897).
(7) Odet and Vignon, *C. R. Acad. Sci., Paris*, **69** [II], 1142 (1869).
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(9) V. Gold, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2467 (1950).
(10) F. Daniels and E. H. Johnston, *J. Amer. Chem. Soc.*, **43**, 53 (1921); H. Eyring and F. Daniels, *ibid.*, **52**, 1472 (1930).
(11) P. B. D. de la Mare, and J. H. Ridd, "Aromatic Substitution. Nitration, and Halogenation," Butterworth and Co. (Publishers) Ltd., London, 1959, p 51 ff.
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(13) J. J. Wren, *J. Chromatogr.*, **4**, 173 (1960); G. J. Young, *J. Colloid Sci.*, **13**, 67 (1958).
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(16) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 90 ff.
(17) K. Fajans and K. von Beckerath, *Z. Physik. Chem.*, **97**, 47 (1921).

65 (5.0), 69 (0.4), 70 (0.6), 72 (0.5), 98 (0.4), 100 (0.1), 121 (0.6), 131 (0.2).

(b) A tightly stoppered sample of $AgNO_3$–silicic acid covered with CCl_4 was allowed to stand for 24 hr. A 1 ml sample of the liquid phase was transferred to a 10-cm path length fused-quartz cell. The uv–visible spectra were recorded using a slit–cell geometry which placed only the vapor above the CCl_4 solution in the light path. The observed spectrum, consisting of *ca.* 40 narrow lines superimposed on broad maxima centered near 340 and 400 mμ, was that reported for NO_2–N_2O_4.[18]

(c) A 3.868-g (4.80 mmol $AgNO_3$) sample of $AgNO_3$–silicic acid was placed in a small chromatographic column arranged to deliver effluent into a solution containing 15 ml of CCl_4 and 1.6 ml of aniline. Flow of carbon tetrachloride through the column was begun, and within 2 min a white precipitate appeared in the magnetically stirred receiver solution. Three fractions were collected using fresh aniline–CCl_4 solutions: effluent volumes in ml (flow times in min) 30 (20), 30 (35), and 65 (110). Each fraction was filtered, and the white solid was washed with water and dried, yielding 230, 34, and 15 mg of carbanilide respectively (total 279 mg, 1.32 mmol, 0.274 mmol $COCl_2$/mmol $AgNO_3$). The combined material was recrystallized (78% recovery) from ethanol, mp 243.5–244°, mmp [with authentic carbanilide (mp 243.5–244°)] 243–243.5°. If the elution is conducted with 10% of benzene in the CCl_4, very little phosgene is produced.

(d) In a similar experiment benzene replaced the aniline of experiment c. The effluent was stirred for 48 hr; analysis by glpc revealed no nitrobenzene.

(e) A 2.336-g (2.89 mmol $AgNO_3$) sample of $AgNO_3$–silicic acid was covered with CCl_4 in a vessel connected to a vacuum line by way of a small trap cooled in liquid N_2. Over a period of 2.5 hr, all of the volatile material was slowly distilled into the trap. The trapped material was warmed to ~−50° and 11 ml of a solution prepared by dissolving 5.07 g of NaOH in 50 ml of water was added. The mixture was allowed to come to room temperature, the phases were equilibrated and separated, and a water wash of the CCl_4 phase was added to the aqueous phase which was then acidified with nitric acid. Gravimetric determination of Cl^- then produced 0.234 g (1.38 mmol) of silver chloride corresponding to 0.69 mmol of $COCl_2$ or 0.24 mmol of $COCl_2$/mmol of $AgNO_3$.

Nitration of Benzene (Expt 1–16).—To the freshly dried $AgNO_3$–silicic acid (or alumina) sample (weight in Table I) was added 10 ml of CCl_4–hexane (1:2). After 1–15 min, 250 μl (214 mg, 2.74 mmol) of benzene was injected and the mixture was agitated and allowed to stand for the specified time. It was then transferred to a small chromatography column and eluted with ether to provide one or two (depending on the amount of silicic acid used) 25.0-ml product solutions which were analyzed by gas chromatography.

(18) T. C. Hall, Jr., and F. E. Blacet, *J. Chem. Phys.*, **20**, 1745 (1952).

Nitration of Anisole (Expt 17–23).—Nitration with excess CCl_4 (expt 17) was done as in the preceding paragraph, substituting anisole for benzene. Nitration with CCl_4 as limiting reagent (expt 19–23) was done by adding 10–20 ml of hexane to the dry, 5–10-g $AgNO_3$–silicic acid sample, injecting 100 μl (150 mg, 0.975 mmol) of CCl_4, and stirring magnetically for the specified time (Table I). Anisole (1.0 ml, 990 mg, 9.1 mmol) was injected and the mixture was stirred for 1 hr, then allowed to stand for 17 hr; work-up was as in the preceding paragraph. The *o*- and *p*-nitroanisole peaks in the gas chromatogram were ~75% resolved, and the isomer ratio was calculated by integration in comparison with standard mixtures.

Nitration by HNO_3–Silicic Acid.—To a slurry of 3.18 g of dry (130–140° overnight) silicic acid in 10 ml of hexane–CCl_4 (2:1) was added 50 μl (73 mg, 1.28 mmol) of white, fuming nitric acid. The mixture was stirred magnetically for 5 min, and 125 μl (107 mg, 1.37 mmol) of benzene was added. The mixture was worked up and analyzed as in the reaction with CCl_4 after 48 (96) hr to give 0.15 (0.17) mmol, 11 (13%), of nitrobenzene.

Application of this procedure to 6.67 g of silicic acid, 16.5 ml of hexane, 73 mg (0.96 mmol) of nitric acid, and 1.0 ml (9.1 mmol) of anisole gave, after 18 hr, 0.29 mmol (31%) of nitroanisoles.

Nitration of 2,4-Dinitrophenol.—A suspension of 500 mg (2.72 mmol) of 2,4-dinitrophenol (mp 112.5–113.5°) in 15 ml of CCl_4 was vigorously stirred with 4.687 g (5.81 mmol $AgNO_3$) of $AgNO_3$–silicic acid for 24 hr. The suspension was filtered and the solid was washed with ether and methanol. The residue from evaporation of the filtrate was dissolved in 25 ml of methylene chloride and extracted with 150 ml of pH 4.4 citrate buffer. The buffer was washed with three 25-ml portions of methylene chloride and the combined organic phases were evaporated to 223 mg (1.21 mmol, 45%) of recovered 2,4-dinitrophenol. The aqueous phase was acidified with 8 ml of sulfuric acid and extracted with four 25-ml portions of methylene chloride which gave on evaporation 306 mg (1.33 mmol, 49%) of picric acid, mp 120–122°, mmp [with authentic material (mp 121–122.5°)] 121–122°; the infrared spectra were identical.

Registry No.—Benzene, 71-43-2; anisole, 100-66-3; silver nitrate, 7761-88-8; carbon tetrachloride, 56-23-5.

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Analysis of Mass Spectral Fragmentation Patterns in Various Bicyclic Alcohols

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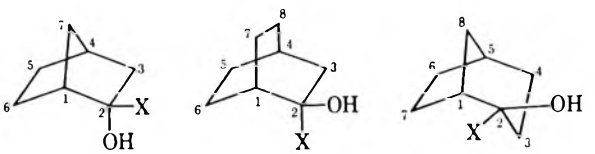
Various bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, and bicyclo[3.2.1]octyl substrates, particularly alcohols and olefins, have been subjected to careful study of their fragment ions occurring in the high-resolution mass spectrometer. The olefins undergo retro-Diels–Alder cleavage as the principal mode of fragmentation. An internal retro-Diels–Alder[1a] fragmentation appears to take place in the [3.2.1]octene ion which does not accommodate a normal class D fragmentation. All the alcohols, including the bridgehead cases, undergo dehydration *via* the formation of an intermediate carbonium ion, which then experiences extensive scrambling of the hydrogen (and deuterium) atoms on the skeleton before completing elimination of the elements of water. The resulting olefin ion then suffers a retro-Diels–Alder fragmentation, but this route is shown to be vitiated as a means of locating the deuterium on the skeleton and tracing the course of rearrangement reactions in solution thereby. It is demonstrated, however, that the *m/e* 57 peak may be applied for this purpose since it is produced in all bicyclic alcohol cases without rearrangement of the skeleton in the mass spectrometer. The manner in which *m/e* 57 (and *m/e* 58 in deuterated cases) arises through fragmentation, the method of locating H and D in bicyclic models, and its use in tracing the course of solvolytic rearrangements are discussed in detail.

Recent studies of carbonium ion rearrangements of bicyclo[3.2.1]-2-octanol and bicyclo[2.2.2]-2-octanol sulfonate esters and analogous derivatives[1b] required application of the mass spectrometer as a means of following the course of reaction. Since more information was needed concerning the fragmentation patterns of bicyclic alcohols, a study was undertaken of the electron-impact fragmentation of the **1**, **2**, and **3** alcohols, the olefins derivable therefrom, and related compounds.



1 **2** **3**

X = hydrogen (normal) or deuterium

In each instance the occurrence of H_2O elimination producing an olefin ion was confirmed by the observation of a metastable peak in the mass spectrum. Two general fragmentation paths were observable, one originating from the parent alcohol and directed by the oxygen containing fragment, the other stemming from the olefin and directed by the double bond.

Results and Discussion

Molecular ions.—The parent peaks of the alcohols (**1**, **2**, **3**) were always readily perceived. They ranged from a low of 1.7% for **1** to a high of 21.5% for **3**. As expected, the corresponding olefins exhibited more intense molecular ion peaks; *e.g.*, 14.7% for bicyclo[2.2.2]octene *vs.* 7.1% for the alcohol **2**. Other investigators have shown[2,3] that in the case of monocyclic alcohols the molecular ion is more intense in the case of equatorial hydroxyl than axial. Such differences, however, though significant in a relative sense, do not appear to be large on an absolute scale. From a practical viewpoint, this did not seem to offer a solution to our problem and no attempt was made to study epimeric differences of this nature.

Retro-Diels–Alder Fragmentations.—This type of mechanism is know to operate in cyclohexenes. Biemann[4] refers to this as a "class D" mechanism and lists two requirements for the operation of the fragmentation mode: (1) the presence of a cyclic olefin or similar system, and (2) the absence of other bonds which might cleave with particular ease *via* certain stated mechanisms. Since bicyclo[2.2.1]-2-heptene (**4**) and bicyclo[2.2.2]-2-octene (**5**) could be prepared *via* Diels–Alder reactions, and since the normal (X = H) alcohols **1** and **2** could dehydrate under mass spectral circumstances to form these olefins, it was assumed that evidence for a retro-Diels–Alder reaction might be found in the mass spectra of **1**, **2**, **4**, and **5**.

The peaks corresponding to this "class D" mechanism actually constitute the major fragment ions of the mass spectra of **4** and **5** (see Figure 1). This observation holds for the spectra obtained at 15 V as well as those obtained at the conventional 70 V. Metastable transition peaks representing these fragmentations were observed at *m/e* 46.3 in the spectrum of **4** and at *m/e* 59.5 in the spectrum of **5**.

The (normal) alcohols **1** and **2** also show evidence of the retro-Diels–Alder fragmentation. The peaks analogous to those in the spectra of **4** and **5**, although not the major peaks of the spectra (see Figures 2 and 3), are still very intense, 20.1% for the *m/e* 66 peak in (normal) **1** and 79.0% for the *m/e* 80 peak in (normal) **2**. In addition, these alcohols also display metastable transition peaks at *m/e* 46.5 in the case of (normal) **1** and *m/e* 59.4 in the spectrum of (normal) **2**. A metastable peak at *m/e* 60.2 in the spectrum of the deuterated (X = D) **2** confirm this fragmentation. This results from the transition $109 \rightarrow 81 + 28$.

On the other hand, *no* metastable peak was detected in the mass spectrum of the [3.2.1] (normal) alcohol **3** (see Figure 4) which could be correlated with fragmentation *via* a "class D" pathway. This is attributable to the absence of structural accommodation for the retro-

(1) (a) H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968). (b) H. Kwart and J. L. Irvine, *J. Amer. Chem. Soc.*, **91**, 541 (1969).

(2) K. Biemann and J. Seibl, *ibid.*, **81**, 3149 (1959).

(3) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 410, 2735 (1967).

(4) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., N. Y., 1962. See also, for further illustrations of the RDA fragmentation in bicyclic compounds, T. Gato, *et al.*, *Tetrahedron*, **22**, 2213 (1966), and W. C. Steele, B. H. Jennings, G. L. Botyos, and G. O. Dudek, *J. Org. Chem.*, **30**, 2886 (1965).

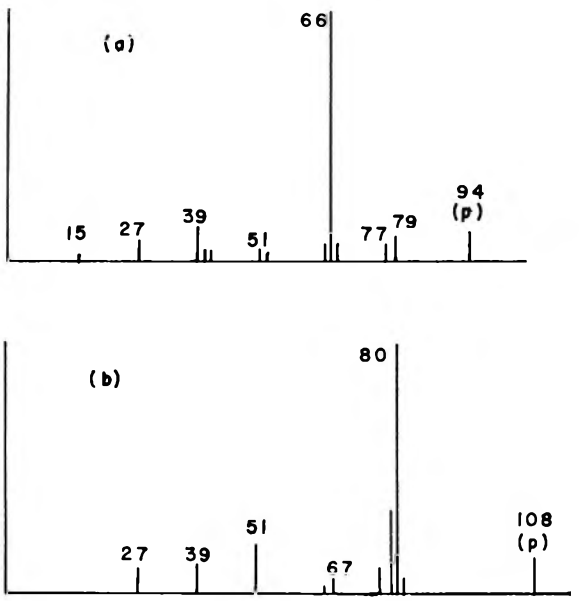


Figure 1.—Mass spectra: (a) bicyclo[2.2.1]-2-heptene (4), (b) bicyclo[2.2.2]-2-octene (5).

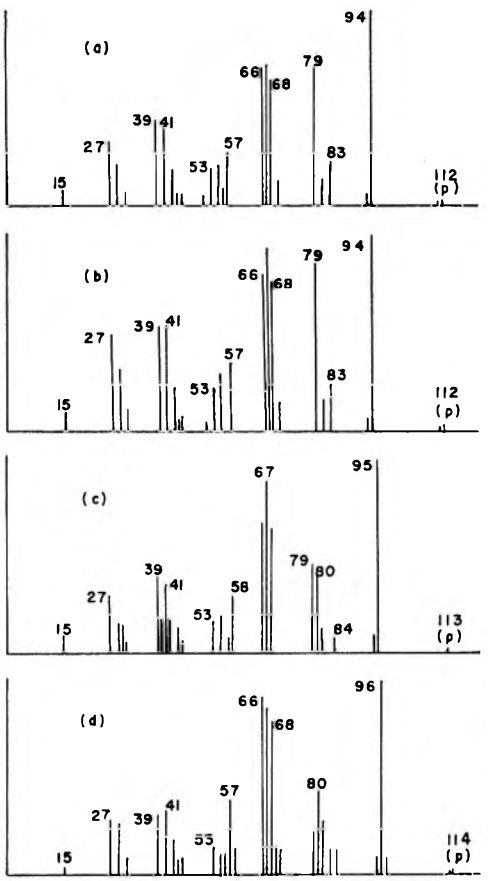


Figure 2.—Mass spectra: (a) bicyclo[2.2.1]-2-heptanol, *endo* (1, X = H); (b) bicyclo[2.2.1]-2-heptanol, *exo;* (c) bicyclo-[2.2.1]-2-heptanol-2-*d*, *endo* (1, X = D); (d) bicyclo[2.2.1]-2-heptanol-3,3-d_2, *endo* (6).

Diels–Alder reactions.[5] However, a major peak (98.7%) was recorded at *m/e* 80 whose constitution was established to be $C_6H_8^+$ (through high-resolution mass determination). This could arise as a result of fragmentation *via* an internal retro-Diels–Alder,[5] a well characterized electrocyclic rearrangement proceeding

(5) See, for a full discussion of this reaction, ref 1a.

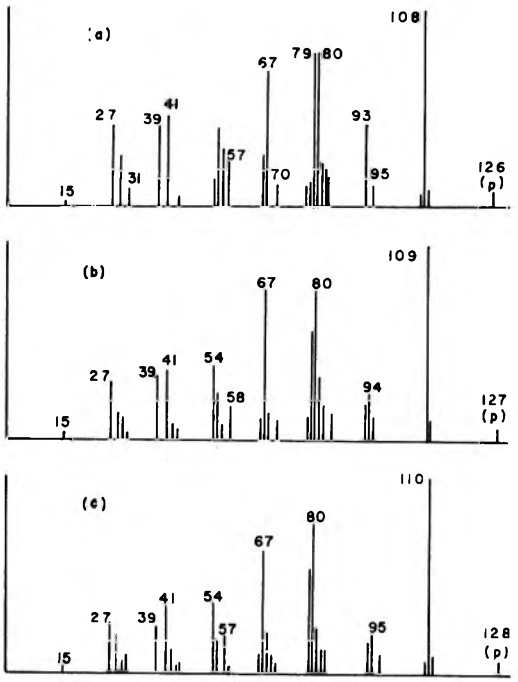


Figure 3.—Mass spectra: (a) bicyclo[2.2.2]-2-octanol (2, X = H); (b) bicyclo[2.2.2]-2-octanol-2-*d* (2, X = D); (c) bicyclo-[2.2.2]-2-octanol-3,3-d_2 (7).

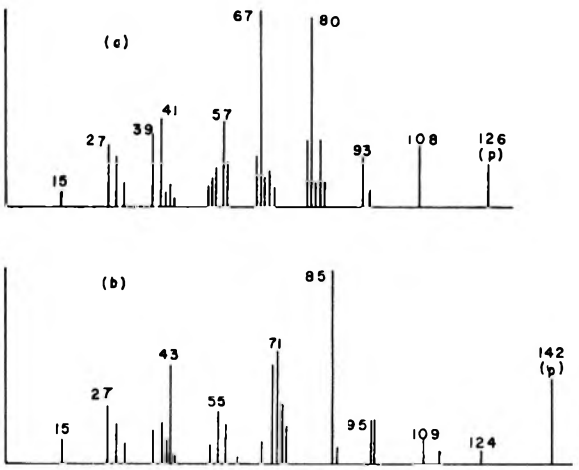
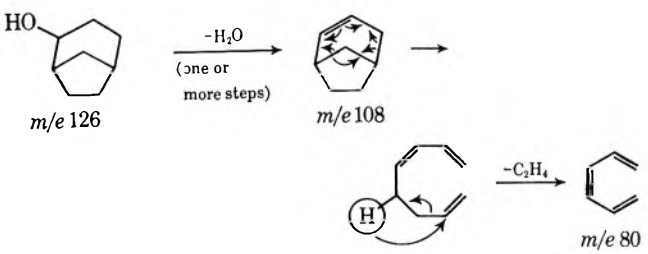


Figure 4.—Mass spectra: (a) bicyclo[3.2.1]-2-octanol (3); (b) bicyclo[2.2.2]-1,8-octadiol (10).

readily under far less energetic circumstances than prevail in the mass spectrometer (as illustrated below).



Dehydration.—The major peak in the spectra of the bicyclic alcohols 1 and 2 and their deuterated analogs is due to the loss of water. In the mass spectrum of the [3.2.1] alcohol, 3 (X = H), the peak due to the loss of a mole of H_2O, although not the major peak of the spectrum, is still very intense (32.6%). Metastable transition peaks establish this fragmentation as due to

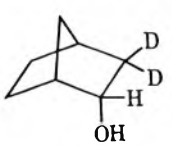
dehydration, since the 18 mass units are lost as a single group.

The loss of water has been demonstrated to occur to varying extents in the spectra of monocyclic alcohols, ranging from approximately 10% in cyclopentanol to 50% in cyclohexanol. Dehydration by way of aldehyde intermediates, which have been shown to fragment with subsequent elimination of water, has been suggested[6] as one possible mechanistic course. However, this path is not functional in any of the bicyclic alcohols under study here. No evidence could be found to confirm the fragmentation of a formyl group from the parent ion.

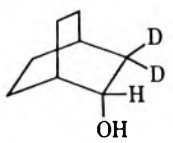
In the case of cyclohexanol, the source of the hydrogen which coupled with the hydroxyl group (comprising the water eliminated) was proven[7] to be distributed around the ring with the exception of the C_1. The failure of the hydroxyl-bearing carbon to yield its other hydrogen to form the water eliminated has been confirmed by our studies. In the spectra (c), Figure 2, of alcohol **1** (X = D) and (b), Figure 3, of **2** (X = D) there is no evidence for the loss of 19 mass units, which could occur if this atom were involved, (HDO in these cases).

The source of the second hydrogen could have been the C_3 if the analogy to an α,β-elimination reaction in solution is fulfilled. The resulting olefin (for example, the bicyclo[2.2.1] heptene ion) could then give rise to a retro-Diels–Alder fragmentation route, as discussed in the previous section of this report.

However, when *endo* bicyclo[2.2.1]-2-heptanol-3,3-d_2, **6**, suffers fragmentation, as is evident from the spectrum (d), Figure 2, the *m/e* 96 (the base peak) is more than ten times as intense as *m/e* 95, indicating



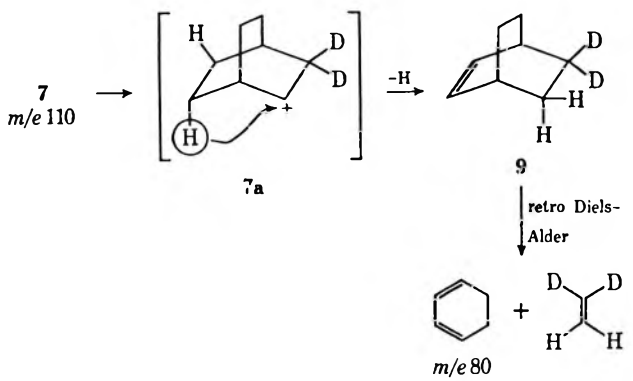
6



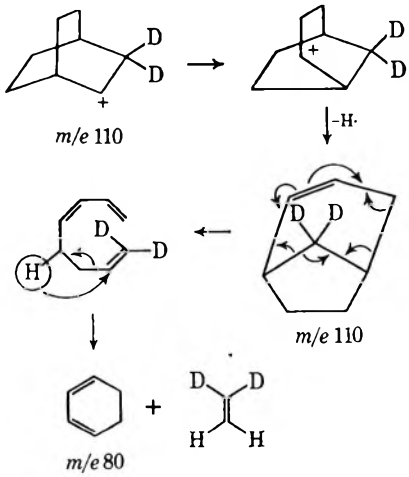
7

that little or no α,β elimination of deuterium has taken place. This confirms an observation briefly reported earlier.[8] Moreover, we have found a nearly identical result in the case of fragmentation of the corresponding [2.2.2]bicyclic alcohol **7**, where the base peak (*m/e* 110) is actually more than twenty times as intense as the peak (*m/e* 109) corresponding to HDO elimination.

Clearly, the loss of hydroxyl from the parent ion in each case (**6** and **7**) has resulted in a carbonium ion in whose structure hydrogen and deuterium positions have become extensively scrambled. Presumably this has occurred through very rapid C—C bond shifting and hydride migrations such as are characteristic of the similarly structured carbonium ions in solution.[1] Ultimately these carbonium ions must lose hydrogen and be converted to the olefin ions **8** and **9**. This is demanded by the retro-Diels–Alder products of fragmentation of **8** and **9**, namely, the formation of cyclopentadiene (*m/e* 66) and cyclohexadiene (*m/e* 80) ions (respectively), through expulsion of a neutral ethylene fragment, which (as pointed out earlier) are very evident in the spectra of the (normal) alcohols **1** and **2**. In the case of **7**, the *m/e* 80, representing the expulsion of $CD_2{=}CH_2$ from the base *m/e* 110, is significantly more intense than *m/e* 81 and 82 (corresponding, respectively, to the expulsion of $CHD{=}CH_2$ and $CH_2{=}CH_2$). Consequently, the structure **9** can be assigned as the preponderant olefin (ion) resulting from dehydration of **7**. Its formation could be readily accomplished in two successive steps involving C—H bond breaking in the intermediate carbonium ion **7a** (illustrated below).



A concomitant path of more than equal likelihood producing expulsion of $CD_2{=}CH_2$ from the intermediate carbonium ion **7a** is the result of very facile rearrangement to the [3.2.1] ion (or its nonclassical equivalent). As indicated earlier, the occurrence of an internal retro-Diels–Alder[5] is a highly probable fragmentation mode, which in the present instance can also account for the observed results (illustrated below).



The mechanism is supported by the fragmentation pattern of the monodeuterio alcohol (**2**, X = D) (see spectrum b, Figure 3), where the ratio of *m/e* 109/80 is nearly identical with the ratio of *m/e* 110/80 in the spectrum of **7**. Furthermore, the ratio of *m/e* 80/79 is almost the same for the deuterated alcohols **2** (X = D) and **7**, but is significantly different for the undeuterated bicyclooctanol shown in spectrum a, Figure 3.

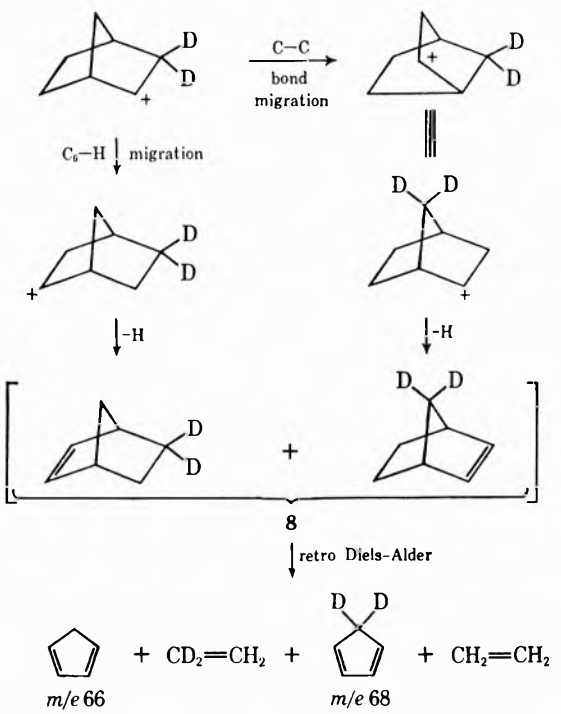
Unfortunately, it is not possible to trace with the same degree of confidence (as in **7**) the course of rearrangement in the corresponding carbonium ion intermediate formed from **6**. The cyclopentadiene ion ($C_5H_5^+$) derived from alcohols is accompanied by a strong $(C_6H_7)^+$ peak and both of these appear to experience extensive protonation (to *m/e* 67 and 68, re-

(6) J. A. Gilpin and F. W. McLafferty, *Anal. Chem.*, **29**, 990 (1957).

(7) P. Natalis, *Bull. Soc. Roy. Sci. Liege*, **31**, 790e (1962). See also C. G. MacDonald, J. S. Shannon, and G. Sugowdz, *Tetrahedron Lett.*, **13**, 807 (1963).

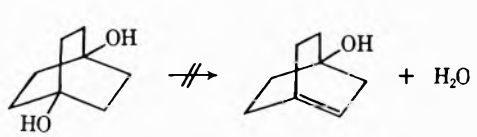
(8) W. Benz and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 2375 (1964).

spectively; see Figure 2) in contrast to the same ion (*m/e* 66) arising from the bicycloheptene directly (see spectrum a, Figure 1). It will be seen, nevertheless, that the *m/e* 66 derived from **6** is of slightly greater intensity than *m/e* 67 and 68, whereas the converse is true of the undeuterated norborneols in Figure 2 (spectra a and c). This would suggest that hydride migration in the carbonium ion derived from **6** through loss of hydroxyl is somewhat more facile. That is to say, this carbonium has a sufficiently greater lifetime than that arising from **7**, allowing for a greater extent of hydride migrations and producing **8**, a more extensively scrambled structure than **9** (as is shown below in classical ion notation).



A parallel observation of the relative lifetimes of these carbonium ions in solution and the significance of this factor in determining the occurrence of C–C and C–H bond migrations have been previously discussed.[1]

Finally, the case of the bridgehead diol **10** will serve as an illustration of the generality of dehydration, even where α,β elimination of the elements of water is most unlikely because the resultant ion would possess the highly strained bridgehead double bond. Nonetheless,



a prominent P − 18 peak is noted in the spectrum (b, Figure 4) of **10**. Similarly the ion product of subsequent retro-Diels–Alder cleavage in the form of the relatively intense peak (24%) at *m/e* 96 is identifiable by high resolution mass determination as $(C_6H_8O)^+$, and its deprotonated satellite (*m/e* 95, 21%). These data can (once again) be reconciled with the occurrence of hydride migration following the formation of the (unstable) bridgehead ion through loss of hydroxyl.

Formation of *m/e* 57 peak.—Another mode of stabilizing the odd-electron molecular ion of an alcohol (supposedly formed by expulsion of a nonbonding electron of an oxygen atom) is through rupture of the C_2–C_3 bond with subsequent decomposition to an *m/e* 57 ion and a hydrocarbon radical. High resolution mass measurements on the bicyclic alcohols studied in this investigation established that the fragment ion of mass 57 has the composition $(C_3H_5O)^+$, probably a resonance stabilized ion of the form $[CH_2{=}CHCHOH]^+$. This is in accord with a conclusion reported earlier[7,9] for cyclohexanol and cyclopentanol.

Although *m/e* 57 is not the major peak of any of the bicyclo alcohols studied here, it is quite intense, comprising 28.6% in **1**, 22.7% in **2**, and 43.9% in **3**. These are shifted to *m/e* 58 in the deuterated analogs with similar peak intensities for corresponding substrates, (*i.e.*, where W = D replaces X = H). Dimmel and Wolinsky[3] have reported *m/e* 57 as the ninth most intense peak in the spectra of both *endo*- and *exo*-norbornanol.

Appropriate labeling of the [2.2.1] and [2.2.2] alcohols established that the initial fragmentation steps in the formation of *m/e* 57 from these alcohols involves the rupture of the C_2–C_3 bond. Thus, deuteration of the hydroxyl-bearing carbon in each case shifted the peaks to *m/e* 58, but complete deuteration of the α (C_3) carbon produced *no shift* of *m/e* 57.

Additional evidence bearing on the course of fragmentation are the metastable peaks at *m/e* 38.9 (calculated 39.1) in the spectrum of the bicyclic alcohol **2** (X = H), and at *m/e* 39.9 (calculated 40.1) of deuterated **2** (X = D). Calculations indicate further that these could be the result of fragmentations which yield peaks at *m/e* 57 and 58, respectively (illustrated below).

$$83 \longrightarrow 57 + 26 \quad (m^* - 39.1)$$

$$84 \longrightarrow 58 + 26 \quad (m^* - 40.1)$$

This would require that there be a prior fragmentation splitting off 43 mass units. Evidence for this occurrence can be found in metastable peaks present in the spectra of **2** (both X = H and X = D).

$$126 \longrightarrow 84 + 43 \quad (m^* \text{ observed } 54.7, \text{ calculated } 54.7)$$

$$127 \longrightarrow 84 + 43 \quad (m^* \text{ observed } 55.6, \text{ calculated } 55.6)$$

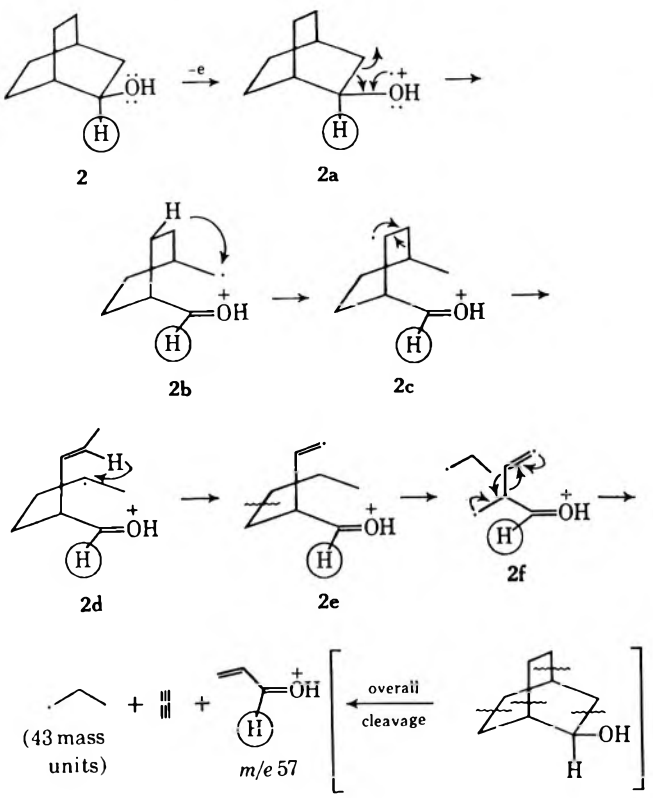
On the basis of these lines of evidence the most likely fragmentation path (**2a** → **2f**) which can be proposed for the bicyclooctanols is that displayed in Scheme I where encircled H traces the hydrogen retained in *m/e* 57.

An analogous fragmentation route (**1a** → **1e**) can be plotted for formation of *m/e* 57 from the bicycloheptanol **1** (see Scheme II) where encircled H traces the hydrogen retained in *m/e* 57.

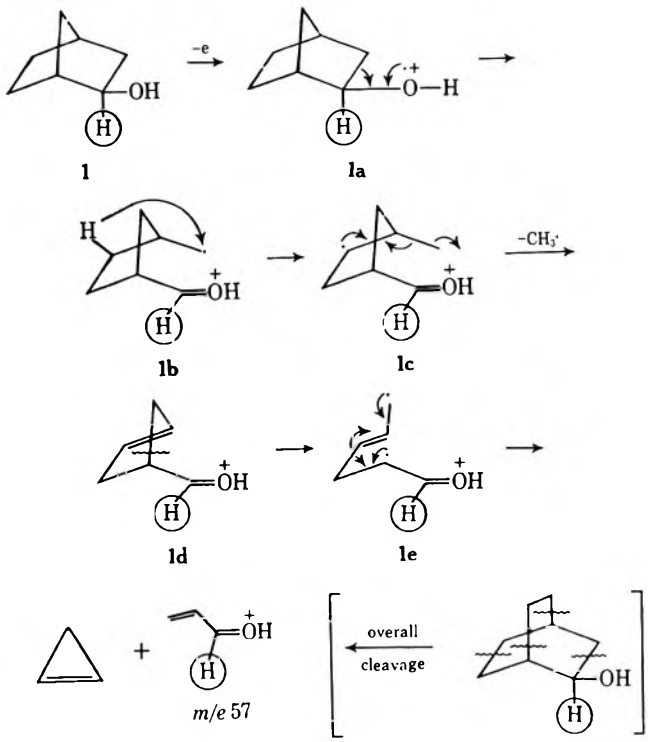
An alternative route leading from **1b** → **1g** (Scheme III) upon rupture of the C_2–C_3 bond is one of the

(9) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964.

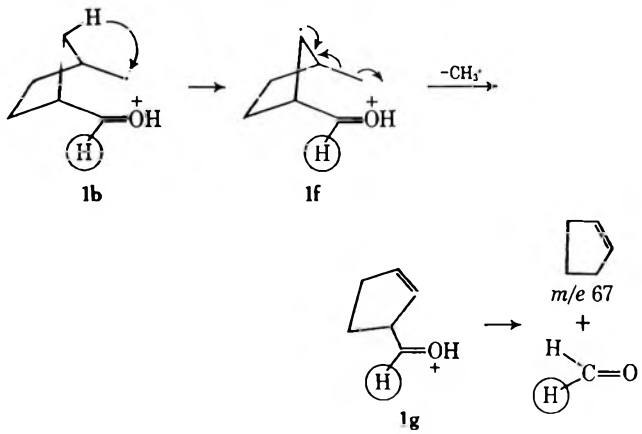
SCHEME I



SCHEME II



SCHEME III



strongest competitors for fragmentation of the parent (along with the dehydration mechanism previously considered). The *m/e* 67, one of the most intense peaks aside from P − 18 in the spectra of all the alcohols in Figure 2, has been shown by high-resolution mass determination to be the pure hydrocarbon ion $(C_5H_7)^+$. The fact that this peak is equally intense in the spectra of all the bicyclo[2.2.1]heptanols, both deuterated and nondeuterated [**1** (X = H), **1** (X = D), and **6**] may be cited as strong evidence supporting this mechanistic proposal. It will also be recognized (see following section of this report) as one of the factors vitiating the application of the retro-Diels–Alder cleavage for locating deuterium on the norbornyl skeleton *via* the *m/e* ratio 66:67.

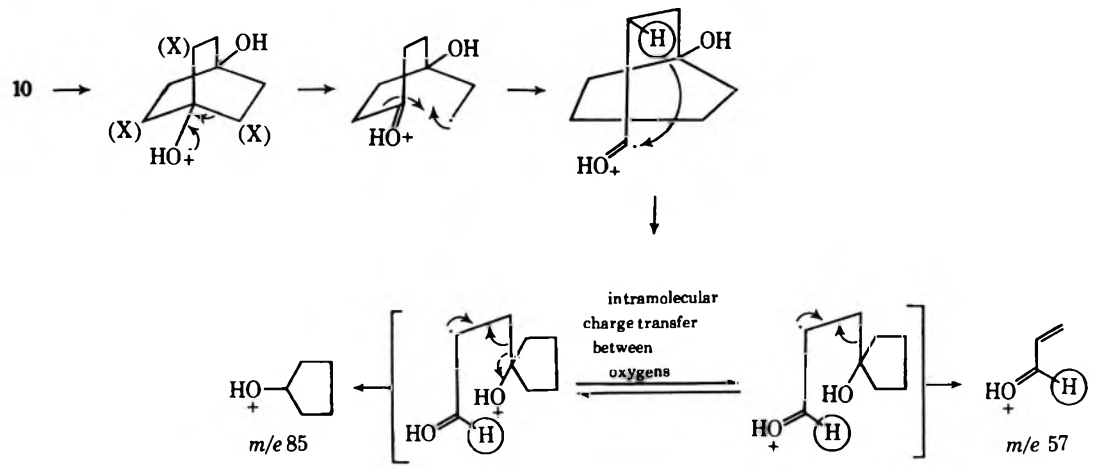
The complete generality of this overall cleavage course in bicyclic alcohol fragmentations leading to *m/e* 57 is to be perceived in the spectrum of the bridgehead diol **10**. In all other (mono) alcohols studied the *m/e* 57 retains the charge [because it has the electronegative oxygen in its $(C_3H_5O)^+$ structure] while losing neutral hydrocarbon fragments in the final cleavage steps. In the diol **10**, however, we observe that the second (hydroxyl) oxygen tends to stabilize the ionic charge, with the consequence that both cleavage fragments can be readily identified as intense peaks; the *m/e* 57 peak is 22% and the *m/e* 85, identified as $(C_5H_9O)^+$, is the most intense (base) peak in the mass spectrum (b), Figure 4. The following (Scheme IV) appears to be the most attractive way of accounting for this result, in consonance, as well, with the fragmentation patterns of the other bicyclic alcohols considered in these studies.

Applications to Deuterium Analysis in Atom-Bridged Compounds.—The migration of deuterium and rearrangement of the carbon skeleton which might be associated with Wagner–Meerwein rearrangements can be followed in certain cases by examination of some of the fragment ions in the mass spectrum. For example, Cristol and coworkers[10] have demonstrated that the retro-Diels–Alder decomposition of dehydronorbornyl acetates provides a way of determining the location of deuterium on the skeleton of this class of bicyclic derivatives. Essentially the method consists of a comparison of the intensities of *m/e* 66 and 67 peaks for estimating the extent of deuterium migration into that part of the molecule which acquires the cyclopentadienyl ion structure in fragmentation of the parent ion.

We have attempted to apply this approach to (saturated bicyclic) norbornyl derivatives which would undergo elimination of HX in the spectrometer. Since fragmentation of the (P − HX) peak to retro-Diels–Alder products is a common occurrence, it seemed likely that a method of deuterium tracing analogous to that used for dehydronorbornyl derivatives could be ap-

(10) S. J. Cristol, R. A. Sánchez, and T. C. Merrill, *J. Org. Chem.*, **31**, 2738 (1966).

SCHEME IV[a]



[a] (X) denotes three equivalent ways in which this fragmentation would occur.

plicable. However (as has been shown earlier in this article), the loss of HOH in the bicyclic alcohols studied was not a simple α,β elimination. Instead, a deep seated rearrangement (in the intermediate carbonium ion) of the hydrogen (and deuterium) atoms of the skeleton attended the loss of hydroxyl. This circumstance clearly obviated the use of any fragment ion which did not contain hydroxyl for purposes of locating deuterium atoms on the skeleton of any saturated bicyclic derivative, particularly the alcohols. Furthermore, as shown in the previous section of this report, the *m/e* 67 peak arises also from one of the most abundant ions in the spectra of norbornyl alcohols independently of deuteration in the C_2 and C_3 positions. This must surely be the most decisive reason why the retro-Diels–Alder cleavage cannot be applied for structure tracing in saturated norbornyl derivatives.

Clearly, then, the only fragment peak which could be used reliably for such trace analysis is one containing the hydroxyl (thereby avoiding the rearrangements stemming from loss of hydroxyl). The *m/e* 57:58 ratio fulfills this specification, both for the bicyclo[2.2.1] and -[2.2.2] alcohols. The substitution of deuterium for the hydrogen on C_2 in each case shifts the bulk of this peak to *m/e* 58. Thus, if, as a result of reaction, the D is "scrambled" out of the C_2 or C_6 positions, this event can be readily detected in all rearrangements of norbornanol derivatives (where the product can be converted to a norbornanol sample for mass spectral analysis).

However, in applying this analysis to rearrangements of bicyclo[2.2.2]octanol derivatives[1] a statistical correction of two must be made for the equivalence of the C_6 and C_7 positions in fragmentation. This can be readily seen in the following illustrative computation. Here the *m/e* 57:58 ratio in a nondeuterated sample corresponds to 100% migration of the deuterium from C_2 while the same measured ratio of 57:58 intensities in the known deuterated, alcohol would represent no deuterium migration from C_2. Thus, the nondeuterated sample of **2** (= 100% D loss) showed a 7.7 (*m/e* 57:58) ratio, while in a sample of **2**, deuterated only at C_2 (= 0% D loss), the measured ratio was 0.22. In a typical acetolysis of the brosylate derivative of the sample deuterated at C_2 the acetate product was purified by glc methods and saponified, and the pure [2.2.2] alcohol recovered in which some of the deuterium had migrated from C_2. The measured ratio of this product was 0.28. This result calculates as

$$2\left[\frac{0.28}{7.7 - 0.22}\right] = 6\% \text{ D migration}$$

Experimental Section

Technique.—The mass spectra of most of the compounds were obtained on a Consolidated Electrodynamics Corp. instrument, Model 21-103-C. Most of the high-resolution fragment ion mass determinations were carried out with a Model 110 instrument. Sample introduction was effected by means of a 350° capacity heated inlet accessory unit. Sufficient volatility of all samples used was realized at inlet temperatures in the range of 150°.

The spectra were obtained usually employing nominal 70-eV ionizing energies except as noted for low voltage spectra where 15-eV ionizing energies were used. The ionizing current could always be adjusted to yield spectra of satisfactory intensity.

Origin of Samples.—We are indebted to John L. Irvine for furnishing the bicyclo[2.2.2]octanol samples (**2**, X = H and X = D). The samples of **6** and **7**, the bicyclic alcohols dideuterated at C_3, were kindly prepared by Dr. Norbert Kucharczyk from the corresponding ketones by three successive base-catalyzed exchanges in dioxane–D_2O media, followed by lithium aluminum hydride reduction to the alcohol, and purification of the product by familiar methods. The samples of **1** (X = H and X = D) were prepared by reduction of the norbornanone using lithium aluminum hydride or deuteride, respectively, adapting the procedures by Brown.[11] Gas chromatographic cuts were ordinarily used to obtain the appropriate mass spectra. The structures of the alcohols and the positions of deuteration, where possible, were always confirmed by nmr and ir analysis.

The samples of bicyclo[2.2.1]-2-heptene (**4**) and bicyclo[2.2.2]-2-octene (**5**) were obtained from Chemical Samples Co., Columbus, Ohio, and were recommended to be greater than 99% purity. The sample of bicyclo[2.2.2]-1,8-octanediol was kindly furnished (in pure form) by Dr. James Kauer. Mass spectra were taken on these samples as received.

Registry No.—**1** (X = H), 497-36-9; **1** (X = D), 24867-16-1; **2** (X = H), 24848-12-2; **2** (X = D), 24867-06-9; **3** (X = H), 5602-48-2; **4**, 498-66-8; **5**, 931-64-6; **6**, 10503-34-1; **7**, 24867-10-5; **10**, 24867-11-6; bicyclo[2.2.1]-2-heptanol, *exo*, 497-37-0.

(11) W. G. Brown, *Org. React.*, **6**, 469 (1951).

The Mechanism of Diphenylketene Cycloaddition to a Carbodiimide[1]

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Received November 5, 1969

Diphenylketene undergoes a 1,2-cycloaddition reaction with diisopropylcarbodiimide in high yield to produce the imino-β-lactam. Quenching the reaction mixture with water results in the formation of N-diphenylacetyl-N,N′-diisopropylurea, diphenylacetic acid, and diisopropylurea as well as the normal adduct. When the cycloaddition is run in liquid sulfur dioxide as the solvent, a near-quantitative yield of 1,1-dioxo-2-(N-isopropylimino)-3-isopropyl-5,5-diphenylthiazolidine-4-one is produced. These results are interpreted to suggest a two-step process *via* a dipolar intermediate in which the second ring closing step is the slow step.

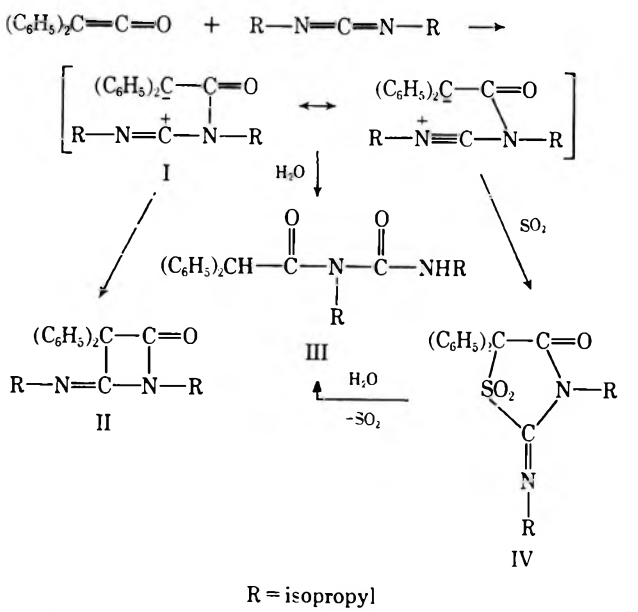
We have recently reported the 1,2 cycloaddition of various types of ketenes with carbodiimides to produce imino-β-lactams.[2] Although the cycloaddition of ketenes across the C=N double bond has been known for many years, the cycloaddition with carbodiimides has only recently appeared, and no reports have been made on the mechanism of this reaction.[3,4] However, several recent communications have indicated that ketene and diphenylketene undergo cycloaddition across the C=N double bond of imines through a two-step process involving a dipolar intermediate.[5-7] These two-step pathways are of course in contrast to ketene cycloadditions to olefins, which are well established to be concerted.[8-13]

We now wish to report evidence for a polar two-step process involving a dipolar intermediate in the cycloaddition of diphenylketene and diisopropylcarbodiimide. A preliminary report of this work has appeared.[14]

Results

Diphenylketene reacts smoothly with diisopropylcarbodiimide in benzene at room temperature to produce the imino-β-lactam (II) in 90% yield.[2,14] The quenching of the above reaction mixture after 4 min with water results in the formation of a 12% yield of N-diphenylacetyl-N,N′-diisopropylurea (III), in addition to the normal adduct (II), diphenylacetic acid, and diisopropylurea. A control experiment proved that III could not be produced from II under the reaction conditions. A second control experiment was also necessary to show that III was not the result of a reaction involving the hydrolysis product of diphenylketene (diphenylacetic acid) and diisopropylcarbodimide. Thus, the reaction of diphenylacetic acid and diisopropylcarbodiimide produced diphenylacetic anhydride and diisopropylurea as expected and none of the urea III.

The reaction of diphenylketene and diisopropylcarbodiimide was also effected employing liquid sulfur dioxide as the solvent. A near quantitative yield of 1,1-dioxo-2-(N-isopropylimino)-3-isopropyl-5,5-diphenylthiazolidine-4-one (IV) was obtained. The hydrolysis of IV produced a quantitative yield of III with the loss of sulfur dioxide. A control experiment revealed that IV could not be produced from II under the reaction conditions.



Discussion

The isolation of III and IV from the respective reaction mixtures as described above is certainly not consistent with a concerted 1,2 cycloaddition. These products are however indicative that this reaction proceeds *via* a dipolar intermediate; *i.e.*, the 1,4-dipolar intermediate is trapped by the addition of water or when formed in liquid sulfur dioxide.

This isolation of such a large amount (12%) of II and a near-quantitative yield of III suggests the dipolar intermediate is relatively long lived. The first step of the cycloaddition must be faster than the second step for such a large amount of the intermediate to build up.

Another interesting possibility for this cycloaddition reaction is that the principle canonical form of the intermediate is V rather than I. Electrostatic considerations would dictate the shape as indicated. Ring clo-

(1) Support of this investigation by the Robert A. Welch Foundation and a National Science Foundation Grant (GP-7386) is gratefully acknowldged.

(2) W. T. Brady, E. D. Dorsey, and F. H. Parry, III, *J. Org. Chem.*, **34**, 2846 (1969).

(3) R. N. Lacey, "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1207.

(4) R. Hull, *J. Chem. Soc. C*, 1154 (1967).

(5) A. Gomes and M. M. Joullié, *Chem. Commun.*, 935 (1967).

(6) H. B. Kagan and J. L. Luche, *Tetrahedron Lett.*, 3093 (1968).

(7) R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem., Int. Ed. Engl.*, **7**, 826 (1968).

(8) T. J. Katz and R. Dessau, *J. Amer. Chem. Soc.*, **85**, 2172 (1963).

(9) R. Huisgen, L. Feiler, and G. Binsch, *Angew. Chem., Int. Ed. Engl.*, **3**, 753 (1964).

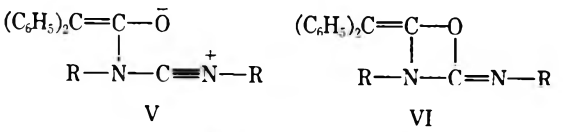
(10) J. C. Martin, W. V. Goodlett, and R. D. Burpitt, *J. Org. Chem.*, **30**, 4309 (1965).

(11) W. T. Brady and H. R. O'Neal, *ibid.*, **32**, 612 (1967).

(12) W. T. Brady and H. R. O'Neal, *ibid.*, **32**, 2704 (1967).

(13) J. A. Baldwin and J. A. Kapecki, *J. Amer. Chem. Soc.*, **91**, 3106 (1969).

(14) W. T. Brady and E. D. Dorsey, *Chem. Commun.*, 1638 (1968).



V VI

sure could occur to yield VI which could be the trapped intermediate, and VI could bleed to the β-lactam II. We looked for VI by spectral, thin layer chromatography, and isolation techniques, but found no evidence suggesting this material was formed. Although this alternative pathway is perhaps possible, we prefer a dipolar species such as I.

It was mentioned above that most ketene cycloadditions to olefins are well established to be concerted processes. Since the system being reported is a two-step process, the change in mechanism is probably due to an enhanced stabilization of the intermediate; *i.e.*, the charges can be adequately stabilized by substituents.

Experimental Section

Benzene was dried by refluxing and distilling from sodium. Isobutyronitrile was dried with 4A molecular sieve. Diphenylketene was prepared by the dehydrochlorination of diphenylacetyl chloride.[15]

3,3-Diphenyl-1-isopropyl-4-isopropyliminoazetidin-2-one (II).—A solution containing 6.4 g (0.033 mol) of diphenylketene and 4.2 g (0.033 mol) of diisopropylcarbodiimide in 100 ml of benzene was allowed to stand at room temperature for 2 hr. Upon removal of the solvent and recrystallization of the solid residue from ether, II was obtained in 88% yield: mp 108.5–109.5°; ir 1810 (C=O) and 1690 cm^{-1} (C=N); nmr (CCl_4) 0.80 (d, 6 H), 1.45 (d, 6 H), 3.66 (m, 1 H), 4.03 (m, 1 H), and 7.3 (m, 10 H).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.7; H, 7.56; N, 8.75. Found: C, 79.0; H, 7.58; N, 8.74.

N-Diphenylacetyl-N,N′-diisopropylurea (III).—A solution containing 6.4 g (0.033 mol) of diphenylketene in 50 ml of benzene was added to a solution of 4.2 g (0.033 mol) of diisopropylcarbodiimide in 50 ml of benzene. This reaction mixture was quenched with 25 ml of water after 4 min. The solvent and water were evaporated on a rotatory evaporator; the residue was dissolved in chloroform. This solution was extracted with a dilute sodium hydroxide solution. Acidification of the basic extract resulted in the crystallization of diphenylacetic acid (47%). The chloroform containing the cycloadduct was evaporated and the residue dissolved in ether. The solution was fractionally crystallized to yield the β-lactam II in 40% yield and the substituted urea III in 12% yield: mp 131–132°; ir 3300 cm^{-1} (N–H) and 1705 cm^{-1} and 1760 cm^{-1} (C=O); nmr (CCl_4) δ 1.13 (doublet 6 H), 1.3 (doublet 6 H), 3.8 (multiplet 1 H), 4.3 (multiplet 1 H), 5.15 (singlet 1 H), and 7.2 (multiplet 11 H).

Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.5; H, 7.75; N, 8.28. Found: C, 74.4; H, 7.82; N, 8.23.

Treatment of Diphenylacetic Acid with Diisopropylcarbodiimide (Control).—To a solution containing 6.4 g (0.003 mol) of diphenylacetic acid in 100 ml of benzene was added 4.2 g (0.033 mol) of diisopropylcarbodiimide. The solution turned brownish yellow with the slight evolution of heat. The solution was quenched with 20 ml of water after 5 min and the mixture stirred for 30 min. The solvent was evaporated and the residue dissolved in chloroform. Diphenylacetic acid was removed from the chloroform solution by extraction with a dilute sodium hydroxide solution. Evaporation of the chloroform solution yielded only diisopropylurea and a small amount of diphenylacetic anhydride. There was no indication N-diphenylacetyl-N,N′-diisopropylurea had been produced.

Cycloaddition of Diphenylketene and Diisopropylcarbodiimide in Sulfur Dioxide (IV).—To a solution of 7.3 g (0.057 mol) of diisopropylcarbodiimide in 125 ml of liquid sulfur dioxide at −78° was added 11 g (0.057 mol) of diphenylketene. The solution was allowed to warm to a gentle reflux at about −10°. After 1 hr, the solvent was removed with an aspirator to yield 20 g (90%) of 1,1-dioxo-2-(N-isopropylimino)-3-isopropyl-5,5-diphenylthiazolidin-4-one (IV): mp 119–122° (gas liberated at melting point); attempts to recrystallize IV resulted in the loss of sulfur dioxide; ir (CCl_4) 1710 (C=O), 1695 (C=N), 1305 cm^{-1} (SO_2); nmr (CCl_4) δ 1.1 (complex set of doublets, J_{HH} = 6 cps, 12 H), 3.7 (multiplet 1 H), 5.0 (multiplet 1 H), and 7.3 (multiplet 10 H); mass spectrum parent peak 384, p-64 (loss of SO_2).

Anal. Calcd for $C_{21}H_{24}N_2SO_3$: C, 65.6; H, 6.3; N, 7.3. Found: C, 65.1; H, 7.0; N, 7.1.

Hydrolysis of 1,1-Dioxo-2-(N-isopropylimino)-3-isopropyl-5,5-diphenylthiazolidin-4-one (IV).—A solution of 2 g of IV in 200 ml of ether was treated with 20 ml of water. The mixture became warm with the evolution of sulfur dioxide. The mixture was warmed on a steam bath until the evolution of sulfur dioxide ceased. The ether layer was separated and evaporated yielding 1.7 g (97%) of N-diphenylacetyl-N,N′-diisopropylurea (III). (For characterization see Experimental Section for III above).

Treatment of 1-Isopropyl-4-isopropylimino-3,3-diphenylazetidin-2-one (II) with Sulfur Dioxide.—A 0.1-g portion of II in 10 ml of liquid sulfur dioxide was allowed to stand at −78° for 24 hr. The solvent evaporated as the reaction vessel was allowed to warm to room temperature. An ir spectrum of the residue was identical with that of II. Thin layer chromatography revealed only one component which had the same R_f value as II.

Registry No.—Diphenylketene, 525-06-4; II, 20452-64-6; III, 21420-67-7; IV, 24867-12-7.

(15) H. Staudinger, *Ber.*, **44**, 1619 (1911).

Photochemistry of Benzophenone Hydrazone

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Benzophenone hydrazone was photolyzed at 2537 and 3000 Å in the presence and absence of air. The reaction is very inefficient with a quantum yield for the disappearance of starting material <0.01. Diphenylmethane is the major photoproduct with benzophenone, benzophenone imine, and benzophenone azine being formed in minor amounts. Triplet sensitization studies indicate that reaction occurs from the singlet state. Mechanisms for the formation of all photoproducts are discussed. Evidence for photooxidation as the principal process in air-exposed photolyses is presented.

Although the photochemistry of carbonyl compounds has been extensively investigated, it is only recently that much attention has been given to the photochemistry of compounds containing the C–N double bond.[1-4] One such account has reported that irradiation under nitrogen of benzophenone hydrazone in methanol through a vycor filter using a 450-W Hanovia high-pressure mercury lamp resulted in substantial conversion to diphenylmethane (25%) and benzophenone (33%) after 2 hr of irradiation.[5] Since our experience with this compound has been quite different, both in regard to reaction efficiency and product ratios, we wish to report the results of an extensive investigation of the photochemistry of this molecule under various reaction conditions.

Results and Discussion

Reaction Conditions.—Samples consisting of 0.2 mmol of hydrazone in 10 ml of solvent were irradiated in quartz tubes at 2537 Å and in Pyrex at 3000 Å. The light source was a Rayonet chamber reactor equipped with a "merry-go-round." All solvents were thoroughly dried before use. Samples were degassed to less than 10^{-4} mm in four to five freeze–thaw cycles. After standing for 5 days, unirradiated samples showed no reaction. All product identities were confirmed by independent synthesis and comparison of spectral data with collected samples.

Products.—The products of the degassed photolysis of benzophenone hydrazone at 2537 Å in methanol, *n*-hexane, and benzene are listed in Table I. Percentage compositions were obtained by vpc analysis using *sym*-tetraphenylethane as an internal standard. Photolyses at 3000 Å resulted in the same products in the same relative proportions; however, owing to the lower source intensity the reaction was much slower at this wavelength.[6] With the concentration of hydrazone used, essentially all incident light was absorbed at both wavelengths. Attempts to determine the quantum yield for the disappearance of hydrazone using potassium ferrioxalate actinometry at 2537 Å were unsuccessful, owing to the inefficiency of the reaction. During the time required for 5% of the hydrazone to disappear, essentially all of the ferrioxalate reacted. The quantum yield of reaction is therefore considerably less than 0.01.

The results of Table I indicate that the major photoproduct is diphenylmethane. The remaining products, benzophenone, benzophenone imine, and benzophenone azine all photolyze at 2537 Å; none, however, yields diphenylmethane as a photoproduct.[7] In order to determine the excited state of the hydrazone responsible for this product, a sensitized reaction using triphenylene as triplet sensitizer was run at 3500 Å. Benzophenone hydrazone is transparent at this wavelength.

Samples of 10:1 triphenylene:benzophenone hydrazone (0.05 *M*:0.005 *M*) in benzene were degassed and allowed to stand 24 hr prior to irradiation to rule out dark reactions. Aliquots were taken every 2 hr, and after 24 hr of exposure, less than half of the hydrazone remained, while sensitizer concentration had not diminished. However, no products could be observed by vpc, and column chromatography yielded only tars in addition to sensitizer and starting material. A control sample without sensitizer had not reacted after 48 hr of irradiation. Moreover, triplet energy transfer was confirmed by the fact that, at concentrations where triphenylene was absorbing essentially all of the light, benzophenone hydrazone quenched triphenylene phosphorescence (EPA, 77°K). Since diphenylmethane is photochemically stable under the sensitized reaction conditions, it was concluded from the above that singlet hydrazone is the excited-state intermediate responsible for the formation of diphenylmethane.

The mechanism of diphenylmethane formation has been described as a photochemical Wolff–Kishner reduction involving an initial hydrogen migration to form the azo compound, followed by loss of nitrogen and radical recombination.[5]

$$(C_6H_5)_2C{=}N{-}NH_2 \xrightarrow{h\nu} (C_6H_5)_2CH{-}H{=}NH \xrightarrow[\text{radical recombn}]{-N_2} (C_6H_5)_2CH_2 + N_2$$

Since it was of interest to us to determine whether the reduction was an entirely intramolecular process,

(1) M. Fischer, *Tetrahedron Lett.*, 5273 (1966).
(2) R. W. Binkley, *J. Org. Chem.*, **33**, 2311 (1968).
(3) E. S. Huyser, R. S. H. Wang, and W. T. Short, *ibid.*, **33**, 4323 (1968).
(4) A. Padwa, W. Bergmark, and D. Pashayan, *J. Amer. Chem. Soc.*, **91**, 2653 (1969).
(5) R. W. Binkley, *Tetrahedron Lett.*, 1893 (1969).
(6) Roughly one-fourth of the starting material reacted in 48 hr in *n*-hexane; 72 hr was required for the same per cent reaction in benzene and methanol.
(7) The photochemistry of benzophenone imine has been studied by E. S. Huyser.[3] Degassed photolyses of benzophenone azine under the outlined reaction conditions resulted only in unreacted starting material and tars.

TABLE I

DEGASSED PHOTOLYSES OF BENZOPHENONE HYDRAZONE AT 2537 Å

Solvent	Time, hr	Products, %[a,b] $(C_6H_5)_2CH_2$	$(C_6H_5)_2CO$	$(C_6H_5)_2CNH$	$(C_6H_5)_2CN_2C(C_6H_5)_2$	$(C_6H_5)_2CNNH_2$	Total
Methanol	4	1.2	Trace	Trace	0.8	98	All
	12	4.0	Trace	Trace	4.0	71.2	79.2
	24	7.6	0.7	1.5	1.8	54.7	66.4
	48	15.9	1.1	2.4	1.5	42.9	63.8
Benzene	4					100	All
	12	1.7	Trace	1.1	1.9	82.5	87.2
	24	2.7	Trace	1.3	1.6	59.0	64.6
	48	6.5	1.0	2.9	1.8	41.9	54.1
n-Hexane	4	1.2	5.4	3.0	3.1	87.3	All
	8	3.1	7.9	5.1	9.2	74.7	All
	12	4.4	7.0	4.0	6.2	47.3	68.9
	20	8.4	6.2	3.8	6.0	18.4	42.8
	24	10.2	5.6	2.8	1.8	13.1	33.5

[a] Based on vpc analysis. [b] Values are accurate to ±10%.

TABLE II

NONDEGASSED PHOTOLYSES OF BENZOPHENONE HYDRAZONE AT 2537 Å

Solvent	Time, hr	Products, %[a] $(C_6H_5)_2CH_2$	$(C_6H_5)_2CO$	$(C_6H_5)_2CNH$	$(C_6H_5)_2CHOCH_3$	$(C_6H_5)_2CN_2C(C_6H_5)_2$	$(C_6H_5)_2CN_2CH_2$	$(C_6H_5)_2CNNH_2$	Total
Methanol	4	Trace	9.5	Trace	1.6	7.4	9.9	59.4	87.8
	8	0.6	8.3	Trace	2.2	14.0	10.5	41.4	77.0
	12	1.6	7.4	1.6	3.0	18.4	6.0	26.7	64.7
Benzene	4	0.8	8.8	4.1		5.8		76.2	95.7
	8	1.4	10.9	4.2		10.4		54.9	81.8
	12	2.5	11.0	4.2		12.2		47.6	77.5
n-Hexane	4	1.3	23.4	9.4		16.2		46.0	96.3
	8	6.6	24.0	7.1		8.3		6.2	52.2

[a] ±10% accuracy.

or whether hydrogen abstraction from solvent was involved, the reaction was run in 99.5% hexadeuteriobenzene. Product analysis was achieved by high resolution mass spectroscopy of a sample whose vpc retention time corresponded to diphenylmethane. The P − 1 peak for pure diphenylmethane (*m/e* 168) is calculated to be approximately 15% the intensity of the parent ion.[8] Sample analysis resulted in a relative intensity of 43%, indicating the presence of monodeuterated diphenylmethane. No evidence for the dideuterated compound was found since the peak at *m/e* 170 was of the expected intensity for a combination of the P + 2 peak of diphenylmethane and the P + 1 peak of the monodeuterated product. These results indicate that hydrogen abstraction from solvent is competitive with radical recombination in the second stage of the reaction. No attempt was made to determine the fate of the phenyl radicals which would be generated by hydrogen abstraction.

Benzophenone, benzophenone imine, and benzophenone azine can result from several competing reaction mechanisms. Benzophenone imine and azine can both be formed by initial cleavage of the N–N bond, followed by radical recombination or hydrogen abstraction from either solvent or starting material.

$$(C_6H_5)_2C{=}N{-}NH_2 \xrightarrow{h\nu} (C_6H_5)_2C{=}N\cdot + \cdot NH_2$$

(radical recombn / H abstraction)

$$(C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2 + H_2NH_2 \qquad (C_6H_5)_2C{=}NH + NH_3$$

(8) R. I. Reed, "Applications of Mass Spectrometry to Organic Chemistry," Academic Press, New York, N. Y., 1966, p 19.

One would also expect to find benzonitrile; however, this product was not observed.

Azine could also be formed by condensation of benzophenone with starting material. Benzophenone can result from the hydrolysis of imine, azine, or starting material, or from direct photooxidation of the latter by residual traces of oxygen in solution. The second process was felt to be significant when solutions were not sufficiently degassed. This conclusion was based upon the previously reported high yield of benzophenone from this photolysis[5] and upon our noticeably higher yields of azine and benzophenone in *n*-hexane (Table I) which is difficult to degas effectively. Therefore, in an effort to verify or eliminate some of the possible reaction routes to these products, nondegassed samples were photolyzed. Results are summarized in Table II.

Photooxidation.—The increased yields of benzophenone listed in Table II are felt to be almost entirely due to photooxidation of starting material. This conclusion is based upon the following evidence. (1) Photolysis of nondegassed benzophenone azine solutions under conditions identical with those used for benzophenone hydrazone produced no benzophenone. A slight amount of decomposition occurred in methanol, the azine completely disappeared with only polymer formation in 24 hr in *n*-hexane and no reaction occurred in benzene. These results are completely consistent with the data in Table II for benzophenone azine. (2) Use of solvents not subjected to further drying gave no change in product ratios, thus eliminating hydrolysis as a significant process.

Condensation of benzophenone with starting material readily explains the increase in benzophenone azine. Somewhat surprising, however, was the observed increase in the rate of formation of diphenylmethane and benzophenone imine in both *n*-hexane and benzene relative to that observed in degassed samples. In addition, two new products, benzhydryl methyl ether and benzophenone azine with formaldehyde, were isolated from the methanol photolysis.

A careful consideration of the above data led to the conclusion that all of these results could be explained by hydrogen abstraction by excited benzophenone and subsequent hydrogen transfer to various species in solution in a process analogous to that observed by Padwa, *et al.*, in the photoreduction of aryl N-alkylimines.[4] In order to test this hypothesis, a benzene solution containing 10:1 benzophenone:hydrazone (mole per cent) was photolyzed at 3500 Å. After 3 hr, less than 15% hydrazone remained (vpc analysis). As had been expected, azine was the major product; however, diphenylmethane (7%) was also present. These two products, together with unreacted ketone and hydrazone, quantitatively accounted for starting material. To rule out possible sensitization by azine, an azine:hydrazone mixture was photolyzed under the same conditions and at 3130 Å. No reaction occurred. The possibility of direct sensitization by benzophenone had been previously eliminated by the results of triphenylene sensitization.

Scheme I outlines the proposed reaction sequence for the air-exposed photolysis of benzophenone hydrazone in methanol. Steps 1 and 2 are the photoprocesses observed in degassed solutions and, owing to their low quantum efficiency, are considered subordinate to steps 3 and 4 in air-exposed solutions. Steps 5–12 list the possible routes for hydrogen abstraction and transfer. Step 5 is likely to predominate in methanol, with step 9 being more significant in solvents where hydrogen abstraction is more difficult. This view is supported by the increase in the rate of diphenylmethane formation in *n*-hexane and benzene. The fact that such an increase is not observed in methanol is explained by the presence of more kinetically favorable reaction paths, such as step 7.

Hydrogen transfer from benzhydroxyl radical to the imino radical, step 6 is felt to be the reason for the observed increase in benzophenone imine. Although reaction between any two of the four radicals in step 6 is theoretically possible, the fact that benzhydrylidenebenzhydrylamine[9] is not formed in any observable amount is attributed to the low efficiency of imino radical formation (Table II).

The presence of benzhydryl methyl ether can only be explained by the mechanism outline in steps 9, 11, and 12. Both the ether and benzophenone azine are known to result from photolysis of diphenyldiazomethane.[10,11]

We conclude from the above that, although it is extremely inefficient, "true" photolysis of benzophenone hydrazone does occur and results primarily in a Wolff–Kishner type reduction to diphenylmethane. This conclusion is based upon the observed slower rate of formation and larger yield of diphenylmethane in degassed solutions, and the fact that, although benzophenone is present in degassed methanol, the amount ($\approx$1%) must be considered insufficient for significant light absorption, since no benzhydryl methyl ether or benzophenone azine with formaldehyde was observed. If, however, oxygen is not scrupulously excluded from the system, the principal result will be photooxidation of starting material to benzophenone with subsequent hydrogen abstraction and transfer by the latter.

SCHEME I

AIR-EXPOSED PHOTOLYSIS OF BENZOPHENONE HYDRAZONE IN METHANOL

A. Primary reactions

(1) $(C_6H_5)_2C{=}N{-}NH_2 \xrightarrow{h\nu} [(C_6H_5)_2CHN{=}NH] \longrightarrow (C_6H_5)_2CH_2 + N_2$

(2) $(C_6H_5)_2C{=}N{-}NH_2 \xrightarrow{h\nu} (C_6H_5)_2C{=}N\cdot + \cdot NH_2 \longrightarrow (C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2 + H_2NNH_2 + (C_6H_5)_2C{=}NH + NH_3$

(3) $(C_6H_5)_2C{=}N{-}NH_2 \xrightarrow{h\nu} [(C_6H_5)_2C{=}N{-}NH_2]^* \xrightarrow{O_2} (C_6H_5)_2C{=}O + H_2O + N_2$

(4) $(C_6H_5)_2C{=}O \xrightarrow{h\nu} [(C_6H_5)_2C{=}O]^*$

B. Secondary reactions

(5) $[(C_6H_5)_2C{=}O]^* + CH_3OH \longrightarrow (C_6H_5)_2\dot{C}OH + H\dot{C}HOH$

(6) $(C_6H_5)_2\dot{C}OH$ (or $H\dot{C}HOH$) $+ (C_6H_5)_2\dot{C}H$ (or $(C_6H_5)_2C{=}N\cdot$) $\longrightarrow (C_6H_5)_2C{=}O + (C_6H_5)_2CH_2$ (or $(C_6H_5)_2C{=}NH + HCHO$)

(7) $(C_6H_5)_2C{=}N{-}NH_2 + HCHO \xrightarrow{h\nu} (C_6H_5)_2C{=}N{-}N{=}CH_2 + H_2O$

(8) $(C_6H_5)_2C{=}O + (C_6H_5)_2C{=}N{-}NH_2 \xrightarrow{h\nu} (C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2 + H_2O$

(9) $[(C_6H_5)_2C{=}O]^* + (C_6H_5)_2C{=}N{-}NH_2 \longrightarrow (C_6H_5)_2\dot{C}OH + (C_6H_5)_2\dot{C}{-}N{=}NH$

(10) $(C_6H_5)_2\dot{C}{-}N{=}NH \longrightarrow (C_6H_5)_2\dot{C}H + N_2$

(11) $(C_6H_5)_2\dot{C}{-}N{=}NH + [(C_6H_5)_2C{=}O]^* \longrightarrow (C_6H_5)_2\dot{C}OH + (C_6H_5)_2CN_2$

(12) $(C_6H_5)_2CN_2 \xrightarrow[CH_3OH]{h\nu} (C_6H_5)_2CHOCH_3 + (C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2 + N_2$

Experimental Section

General.—All melting points are uncorrected and were determined using a Mel-Temp apparatus. Infrared spectra were obtained using a Beckman IR-4 instrument. Liquid samples were run as neat films and solids were run in liquid cells with carbon tetrachloride as solvent. Nmr spectra were recorded on a Varian HR-60 spectrometer in deutero chloroform with tetramethylsilane as internal standard. Mass spectral analyses of photoproducts were performed by Battle Memorial Institute, Columbus, Ohio. All commercial chemicals used were Matheson Coleman and Bell products, and all solvents were Spectrograde. The latter were dried by the following methods: (1) benzene was allowed to stand over sodium for at least 24 hr before use, (2) *n*-hexane was placed over molecular sieve, (3) methanol was

(9) See reference in footnote 7.

(10) H. Staudinger, E. Anthes, and F. Pfenninger, *Ber.*, **49**, 1936 (1916).

(11) W. Kirmse, L. Horner, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **614**, 19 (1958).

distilled over magnesium according to the procedure of Fieser,[12] and (4) deuteriobenzene was distilled and dried over molecular sieve.

Benzophenone Hydrazone.—The extraction thimble of a Soxhlet extractor was filled with 20 g of molecular sieve; 9.1 g (0.050 mol) of benzophenone and 8.8 g (0.176 mol) of 99–100% hydrazine hydrate were refluxed overnight (16–24 hr). The hot alcoholic solution was filtered, and evaporation of solvent yielded 7.2 g (73%) of crude product, mp 90–94°. After one recrystallization from ethanol, the product melted at 98–99° (lit.[13] mp 97–98°).

Photolysis of Benzophenone Hydrazone.—Samples consisting of 0.2 mmol of hydrazone in 10 ml of solvent were irradiated in a Rayonet chamber reactor equipped with a "merry-go-round," at 2537 and 3000 Å. Degassed samples were evacuated to 10^{-5}–10^{-4} mm in four to five freeze–thaw cycles on a high-vacuum line, and helium was pumped through the samples for 5 min after the final cycle. Sample tubes were sealed with a high-vacuum stopcock. Aliquots were periodically withdrawn for vpc analysis through a side arm equipped with serum cap. Analyses were carried out on a Varian Model 1200 flame ionization gas chromatograph using a 5 ft × 1/8 in. column packed with 3% SE-30 on 100/120 Varaport 30. Samples for product identification were collected by column chromatography on Florisil and by preparative vpc on a Varian Model 700 using a 10 ft × 3/8 in. 10% SE-30 on 30–60 Chromosorb W column.

Diphenylmethane and benzophenone were identified by comparison of vpc retention times and ir and nmr spectra with those of commercial samples.

Benzophenone azine was prepared according to the procedure of Szmant and McGinnis, mp 163–164° (lit.[13] mp 164°). A mixture melting point with a sample of photoproduct collected by column chromatography showed no depression, and the infrared spectra of the samples were identical.

Benzophenone imine was prepared from the Grignard reaction of phenyl bromide and benzonitrile,[14] bp 85–86° (0.2 mm) [lit.[14] bp 127° (3.5 mm)]. Infrared spectra of prepared and collected samples had characteristic bands at 3.1 and 6.4 (NH) and 6.25 μ (C=N).

Benzhydryl methyl ether, prepared according to the method of Welch and Smith,[15] had bp 129–130° (2 mm) [lit.[15] bp 153.2–153.5 (14.5 mm)]. The infrared spectrum was identical with that of the photoproduct ether, showing strong CO absorption at 9.1 μ.

Benzophenone azine with formaldehyde was prepared by a procedure similar to that used for starting material. Refluxing 0.8 g (0.004 mol) of benzophenone hydrazone with 0.25 g (0.008 formula wt) of paraformaldehyde in 20 ml of methanol in a Soxhlet extractor (molecular sieve) for 3 hr resulted in a quantitative yield of benzophenone azine with formaldehyde, bp 97–98° (0.03 mm), ir 3.34 and 3.42 (CH_2), and 5.98 and 6.25 μ (C=N). The nmr resonance peak for the methylene group was not observed and was felt to be part of the phenyl multiplet at δ 7–8, since no other peaks were present in the spectrum.

Quantum Yield Studies.—A 0.006 *M* solution of potassium ferrioxalate, prepared according to the method of Calvert and Pitts,[16] and a 0.002 *M* degassed solution of benzophenone hydrazone in methanol were simultaneously irradiated for 2 hr through a 2540 Å band-pass filter using a 450-W Hanovia high-pressure mercury lamp. During this time, <5% of the hydrazone and >95% of the ferrioxalate reacted, and it was therefore impossible to accurately determine the reaction quantum yield by this technique.

Sensitization Studies.—All sensitized reactions were carried out with a 10:1 concentration ratio of sensitizer:hydrazone. Benzene solutions of triphenylene and hydrazone were degassed to $<5 \times 10^{-5}$ mm and allowed to stand 24 hr prior to irradiation. Photolyses at 3500 Å were run in a Rayonet reactor. Azine–hydrazone mixtures were photolyzed using the Hanovia lamp with a 3130-Å band-pass filter.

Registry No.—Benzophenone hydrazone, 5350-57-2.

Acknowledgment.—The authors wish to thank Dr. Roger Foltz, Battelle Memorial Institute, Columbus, Ohio, for his mass spectral analyses.

(12) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, p 289.
(13) H. H. Szmant and C. McGinnis, *J. Amer. Chem. Soc.*, **72**, 2890 (1950).
(14) P. L. Pickard and T. L. Tolbert, *J. Org. Chem.*, **26**, 4886 (1961).
(15) C. M. Welch and H. A. Smith, *J. Amer. Chem. Soc.*, **72**, 4748 (1950).
(16) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York N. Y., 1966, p 785.

Photochemistry of Thiophenes. IX.[1] Rearrangements of Alkylthiophenes and the Dithienyls

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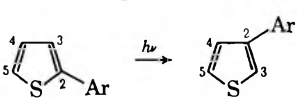
Irradiation of 2-methyl-, benzyl-, neopentyl-, and *t*-butylthiophenes leads to their irreversible transformation to the corresponding 3-substituted derivatives. Yields vary from 8 to 27%. 2,5-Di-*t*-butylthiophene rearranges irreversibly to 2,4-di-*t*-butylthiophene which compound is remarkably stable under the reaction conditions. Irradiation of 2,2′-dithienyl leads to 2,3′-dithienyl and a small amount of benzo[*b*]thiophene. 2,3′-Dithienyl affords 3,3′-dithienyl and benzo[*b*]thiophene as major products. 5,5′-Dideuterio-2,2′-dithienyl gives 5,5′-dideuterio-2,3′-dithienyl upon irradiation while 2′,5-dideuterio-2,3′-dithienyl gives 2,5′-dideuterio-3,3′-dithienyl and 4,7′-dideuteriobenzo[*b*]thiophene. A valence bond isomerization reaction is proposed to account for the results.

We reported previously that arylthiophenes transpose ring atoms upon irradiation.[2] For 2-arylthiophenes these valence bond isomerizations are characterized both by an *irreversible* interchange of the 2- and 3-carbon atoms of the thiophene ring (eq 1) and maintenance of structural integrity in the migrating substituent.



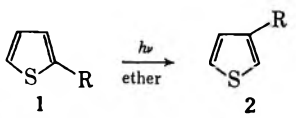
(1)

Experiments with arylalkyl-disubstituted thiophenes indicated that the aryl group migrates in preference to the alkyl group.[3] In this paper we show that simple alkylthiophenes may also rearrange, although usually in somewhat lower yield. Moreover, we find that heteroaromatic substituted thiophenes (*i.e.*, dithienyls) undergo photochemical interconversion.

(1) Paper VIII: R. M. Kellogg and H. Wynberg, *Tetrahedron Lett.*, 5895 (1968).
(2) H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis, *J. Amer. Chem. Soc.*, **89**, 3501 (1967), for a summary.
(3) H. Wynberg, G. E. Beekhuis, H. van Driel, and R. M. Kellogg, *ibid.*, **89**, 3498 (1967).

Results

Thiophenes with alkyl substituents in the 2 position rearrange upon irradiation to give the corresponding 3-substituted isomers (eq 2). The yields given are

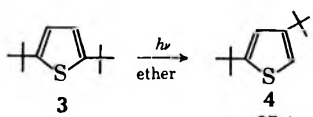


(2)

1	2
a, R = CH_3	8-9%
b, R = $CH_2C_6H_5$	15%
c, R = $CH_2C(CH_3)_3$	10%
d, R = $C(CH_3)_3$	27%

based on consumed starting material; intractable solids account for the balance of products. Irradiation of the 3-substituted isomers **2a–d** led to their decomposition; no isomeric products could be detected.

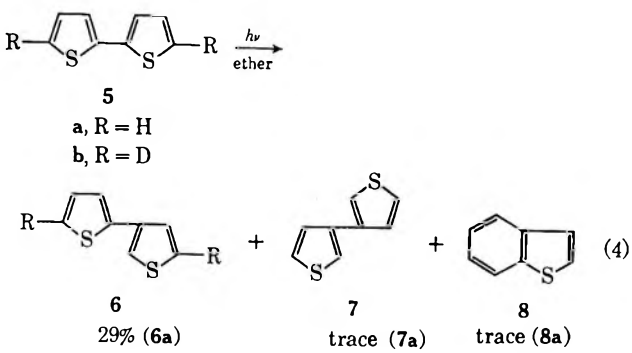
Rearrangement of 2,5-di-*t*-butylthiophene (**3**) took place to give 2,4-di-*t*-butylthiophene (**4**) (eq 3). Re-



(3)

markably, **4**, under a variety of conditions, failed to rearrange and, moreover, seemed to be unusually stable to irradiation (see Experimental Section).

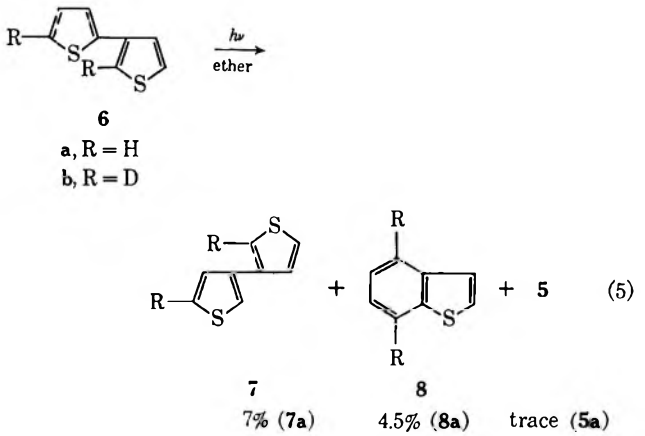
Some significant deviations in behavior were observed with the dithienyls. Irradiation of 2,2′-dithienyl (**5a**) yielded 2,3′-dithienyl (**6a**) as the major product with trace amounts of 3,3′-dithienyl (**7a**) and benzo[*b*]thiophene (**8a**) (eq 4). Irradiation of **5b**, wherein deute-



(4)

rium has been substituted for hydrogen at the 5,5′-position,[4] led to the same products. The rearranged product **6b** was identified as 5,5′-dideuterio-2,3′-dithienyl. The spectral properties of all deuterated compounds[6] are given in detail in the Experimental Section. Owing to the low yield the products **7b** and **8b** could not be isolated. The recovered starting material **5b** had not been observably isomerized.[7]

Irradiation of 2,3′-dithienyl (**6a**) leads to 3,3′-dithienyl (**7a**) and benzo[*b*]thiophene (**8a**) as the major products with a trace amount of 2,2′-dithienyl (**5a**) (eq



(5)

5). Yields are abnormally low owing to the excessive irradiation time used in the preparative experiment. When 2′,5-dideuterio-2,3′-dithienyl (**6b**) was irradiated, the major products were 2,5′-dideuterio-3,3′-dithienyl (**7b**) (*ca.* 90% this isomer) and 4,7-dideuteriobenzo[*b*]-thiophene (**8b**) (*ca.* 80% this isomer) plus a trace quantity of 2,2′-dithienyl. The nmr spectrum of **8a** was solved using the published complete analysis of the benzo[*b*]thiophene spectrum as a guide.[8]

Neither 3,3′-dithienyl (**7a**) nor any of its deuterated isomers gave any photochemical reaction other than decomposition. Considerable care must be exercised in handling deuterated isomers of **7a** as well as other deuterated dithienyls since they have a propensity to lose deuterium under extremely mild acid-catalyzed conditions leading to erroneous interpretations of nmr spectra.[9] This problem is especially pronounced with 2,2′-dideuterio-3,3′-dithienyl.

Some brief investigations of the effects of solvents on the photochemical reactions of the dithienyls were made. Low yields precluded determination of the quantum yields of products but the quantum yield for disappearance of starting material in various solvents could be measured. Qualitatively, the rate of consumption of 2,2′- and 2,3′-dithienyl increased in the following order: ethanol < ether < cyclohexane (see Table I below).

TABLE I

QUANTUM YIELDS FOR DISAPPEARANCE OF DITHIENYLS IN VARIOUS SOLVENTS

Dithienyl	Solvent	Φ_d
2,2′	Ether	0.07
2,2′	Ethanol	≤0.01
2,2′	Cyclohexane	0.10
2,3′	Ether	0.07
2,3′	Ethanol	0.05
2,3′	Cyclohexane	0.09
3,3′	Ether	0.12
3,3′	Cyclohexane	0.16

(4) The results with the dithienyls were discussed at the Second IUPAC Symposium on Photochemistry, Enschede, The Netherlands, July 1967; the use of deuterium in elucidation of rearrangement paths in arylthiophenes has been described previously.[5] The methods used in the syntheses of the deuterated dithienyls have been published separately.[6]

(5) R. M. Kellogg and H. Wynberg, *J. Amer. Chem. Soc.*, **89**, 3495 (1967).

(6) R. M. Kellogg, A. P. Schaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, **33**, 2902 (1968).

(7) Observable scrambling of the deuterium label in starting material does occur when 2-pentadeuteriophenyl-5-deuteriothiophene is irradiated.[4]

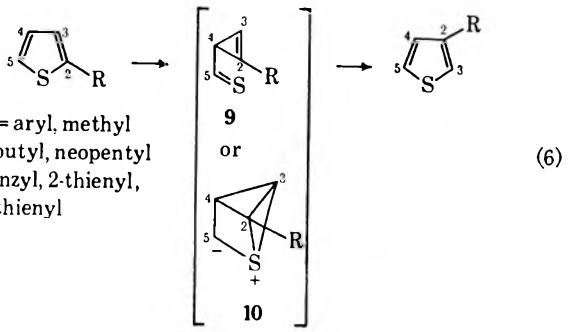
(8) K. Takahashi, I. Ito, and Y. Matsuki, *Bull. Chem. Soc. Jap.*, **39**, 2316 (1966).

(9) R. M. Kellogg, A. P. Schaap, and H. Wynberg, *J. Org. Chem.*, **34**, 343 (1969).

In ethanol solution, 2,2′-dithienyl was so stable that its rate of disappearance could scarcely be observed even using long irradiation periods.

Discussion

In an earlier publication[2] we suggested that the irreversible rearrangement of 2-aryl to 3-arylthiophenes involved at some stage either cyclopropenylthioaldehyde (**9**) or sulfur valence-shell expanded bridged structures (**10**) (eq 6).[10] Our sentiments lay with **10** which



(6)

we felt was an excited- rather than a ground-state intermediate. We later observed that various dienes caused inhibition of the 2-phenyl to 3-phenylthiophene rearrangement, led to quenching of 2-phenylthiophene fluorescence, and added photochemically to 2-phenylthiophene.[1] All these reactions were shown to involve an excited singlet state of 2-phenylthiophene.

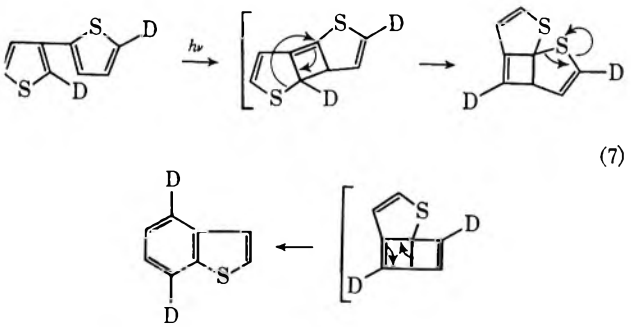
The rearrangements described in this paper complement previously accumulated data on arylthiophenes and illustrate the ubiquity of these thiophene rearrangements.[11] The irreversibility of rearrangement, retention of structural integrity of the migrating substituent, and failure to isolate intermediates are trademarks of thiophene photorearrangements. Unfortunately, the present results allow no choice between intermediates **9** and **10**. This choice may be academic, however, since **9** and **10** could easily be two equivalent graphic representations of the same *excited-state* intermediate.

(10) A number of reports of photochemically induced valence bond isomerizations have appeared recently. The following list is representative—(a) pyrazine to pyrimidine: F. Lahmani and N. Ivanoff, *Tetrahedron Lett.*, 3913 (1967); (b) isothiazole to thiazole: J. P. Catteau, A. LaBlanche-Combier, and A. Pollet, *Chem. Commun.*, 1018 (1969); (c) imidazoles: H. Tiefenthaler, W. Dörscheln, H. Göth, and H. Schmidt, *Helv. Chim. Acta*, **50**, 2244 (1967); (d) imidazoles and pyrazoles: P. Beak, J. L. Miesel, and W. R. Messer, *Tetrahedron Lett.*, 5315 (1967); (e) 1,3,5-tri-*t*-butylbenzene in solution: I. E. Den Besten, L. Kaplan, and K. E. Wilzbach, *J. Amer. Chem. Soc.*, **90**, 5868 (1968); (f) 1,3,5-benzene-d_3 in gas phase: K. E. Wilzbach, A. L. Harkness, and L. Kaplan, *ibid.*, **90**, 1116 (1968); (g) references, through early 1967 are given in ref 2. Stable ring-opened intermediates have been obtained in some cases; (h) poly-*t*-butylfurans in solution: E. E. van Tamelen and T. H. Whitesides, *J. Amer. Chem. Soc.*, **90**, 3894 (1968); (i) azirine intermediates from 3,5-diphenylisoxazole: B. Singh and E. F. Ullman, *ibid.*, **89**, 6911 (1967), and E. F. Ullman and B. Singh, *ibid.*, **88**, 1844 (1966); (j) for further isoxazole reactions see M. Kojima and M. Maeda, *Tetrahedron Lett.*, 2379, 1969; (k) ring-opening has been postulated in gas phase irradiations of furans: R. Srinivasan, *J. Amer. Chem. Soc.*, **89**, 1758 (1967); (l) R. Srinivasan, *ibid.*, **89**, 4812 (1967); (m) H. Hiraoka and R. Srinivasan, *ibid.*, **90**, 2720 (1968); (n) ring-opening is also observed in dihydrofurans: P. Scribe, M. R. Monot, and J. Wieman, *Tetrahedron Lett.*, 5157 (1967); (o) D. W. Boykin, Jr., and R. E. Lutz, *J. Amer. Chem. Soc.*, **86**, 5046 (1964).

(11) To be on completely safe ground, one would have to identify the position of every carbon atom after rearrangement in each example and to establish that the migrating substituent never departs from the carbon atom to which it is bound in the starting material. The point of diminishing returns is quickly reached in such research, however, and we are inclined to accept results established with arylthiophenes as articles of faith for the present examples.

Noteworthy is the observation that thiophene, when irradiated (unsensitized) in the gas phase, yields ethylene, allene, methylacetylene, carbon disulfide, vinylacetylene, and polymeric material. Cyclopropene, a likely product from thiodecarbonylation of cyclopropenylthioaldehyde, is conspicuously absent.[12] On the other hand, cyclopropene is one of the major products formed during (sensitized) gas phase irradiation of furan.[10k]

Two departures from the expected rearrangement pattern deserve comment.[13] First, the rearrangement of 2,5′-dideuterio-2,3′-dithienyl (**6b**) to chiefly 4,7-dideuteriobenzo[*b*]thiophene (**8b**) (in addition to the 3,3′-dithienyl **7b**) must involve an involved recombination of atoms. A possible mechanism, not involving hydrogen (deuterium) shifts, is shown in eq 7. A different route



(7)

must be followed in the formation of benzo[*b*]thiophene from 2,2′-dithienyl, but the small amount formed and absence of labeling data prevent speculation regarding its origin. This product does appear, however, simultaneously with 2,3′-dithienyl indicating it *not* to be a secondary irradiation product of the latter compound.

A second anomaly is the absence of rearrangement of 2,4-di-*t*-butylthiophene. Were rearrangement to take place, the thus far unknown 3,4-di-*t*-butylthiophene (**11**)

11

would be formed. It is tempting to suppose that a sufficiently high barrier is met in passing to this necessarily highly strained system[14] that the intermediate simply drops back to starting material and does so with efficiency. The rearrangements to the respective 3,4-disubstituted thiophenes proceed with 2,4-diphenylthiophene[15] and 4-methyl-2-phenylthiophene;[3] here, however, much smaller groups are involved.

Experimental Section

Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 instrument in the specified solvent using tetramethylsilane (TMS) as internal standard. Ir spectra were run on a Perkin-Elmer 257 instrument. Analytical gas–liquid chromatography (glpc) was carried out on a F & M Model 810 gas

(12) H. A. Weibe and J. Heicklen, *Can. J. Chem.*, **47**, 2965 (1969).

(13) An interesting deviation has been reported. Irradiation of either 2- or 3-methylthiophene in primary amines gives pyrroles in unreported yield. The mechanism is unclear: A. Couture and A. LaBlanche-Combier, *Chem. Commun.*, 524, 1969.

(14) For a leading reference on the structure and strain of *o*-di-*t*-butyl heteroaromatics, see G. J. Visser, A. Vos, Ae. de Groot, and H. Wynberg, *J. Amer. Chem. Soc.* **90**, 3253 (1968).

(15) H. Wynberg, H. van Driel, R. M. Kellogg, and J. Buter, *ibid.*, **89**, 3487 (1967).

chromatograph equipped with hydrogen flame detectors. Preparative separations were done on a Wilkens A-700 Autoprep or on a F & M 775 Prepmaster.

Irradiations were carried out with lamps previously described. Compounds cited without reference were prepared by standard, published procedures. In particular, the syntheses of the deuterated dithienyls used in this study have been described earlier.[9]

2-Benzylthiophene[16a] was prepared by Wolff–Kishner reduction of 2-benzoylthiophene.[16b,17,18]

3-Benzylthiophene was prepared by the di-*t*-butyl peroxide induced addition of toluene to maleic anhydride to give α-benzylsuccinic anhydride which was treated with P_4S_7 to give 3-benzylthiophene: bp 152° (44 mm), $n^{20}D$ 1.5929 [lit.[20,21] bp 135–137° (17 mm); $n^{20}D$ 1.5928]; and nmr (C_3D_6O) δ 3.88 (s, 2, CH_2) and 7.0–7.5 (m, 8, aromatic).

2-Neopentylthiophene was prepared by allowing thiophene (6.4 g, 0.08 mol) in benzene (80 ml) to react with pivaloyl chloride (10 g, 0.08 mol) in the presence of $SnCl_4$ (20.8 g, 0.08 mol).[22] After several hours of standing the reaction mixture was poured into H_2O; the benzene layer was separated and was washed with H_2O and thereafter was dried over $MgSO_4$. Removal of the benzene and distillation gave 8.75 g (62%) of *t*-butyl-2-thienyl ketone, bp 115° (13 mm), $n^{20}D$ 1.5303. A single *t*-butyl peak at δ 1.37 in the nmr spectrum established that only the 2-isomer had been formed. Wolff–Kishner reduction of the ketone gave 2-neopentylthiophene: bp 185–186 (atm); $n^{20}D$ 1.4945; nmr (C_3D_6O) δ 0.94 [s, 9, $(CH_3)_3C$], 2.72 (s, 2, CH_2), 7.0–7.5 (m, 3, thienyl protons); uv (96% ethanol) λ_{max} 236 (ε 8050).

Anal. Calcd for $C_9H_{14}S$: C, 70.07; H, 9.14; S, 20.78. Found: C, 70.14; H, 9.15; S, 20.54.

2-*t*-Butylthiophene, 3-*t*-butylthiophene, and **2,5-di-*t*-butylthiophene** were obtained by either distillation with a spinning-band column or by preparative glpc on mixtures obtained from the *t*-butylation of thiophene.[24]

2,4-Di-*t*-butylthiophene was obtained by allowing a 20-g mixture of 2,5- and 2,4-di-*t*-butylthiophene[24] to stand for 16 hr (with occasional shaking) in 75–100 ml 96% H_2SO_4. Work-up and distillation gave 2,4-di-*t*-butylthiophene: bp 221–223° (atm); $n^{20}b$ 1.4903 [lit.[24] bp 220° (atm); $n^{20}D$ 1.4916]; nmr (C_3D_6O) δ 1.37 [s, 9, $(CH_3)_3C$], 1.27 [s, 9, $(CH_3)_3C$], 6.68 (d, 1, J = 1.5 Hz, ring proton), 6.61 (d, 1, J = 1.5 Hz, ring proton).

Irradiation of 2-methylthiophene was carried out with a total of 7.2 g (0.073 mol) as a 10^{-2} *M* solution in ether using a Rayonet reactor equipped with 2540 Å lamps. After 9 hr 25% of the starting material was consumed and the remaining material consisted of 3% 3-methylthiophene and 97% 2-methylthiophene. Preparative glpc (Carbowax 20M, 8 ft, 103°) allowed the isolation of 3-methylthiophene which was identified from its nmr spectrum.

Irradiation of 2-benzylthiophene was carried out with 2.66 g (0.0153 mol) as a 5.8×10^{-3} *M* solution in ether using a high pressure Hg lamp. After 8 hr 50% of the starting material had been consumed and the remaining material consisted of 30% 3-benzylthiophene and 70% 2-benzylthiophene. Preparative glpc (Carbowax 20M, 8 ft, 176°) was only partially successful resulting in enrichment of the 3-benzylthiophene fraction. The nmr and ir spectra of this mixture were identical with those of an authentic mixture of 2-benzyl- and 3-benzylthiophene of the same composition.

Irradiation of 2-neopentylthiophene was carried out with a total of 1.80 g (0.0117 mol) as a 6.5×10^{-3} *M* solution in ether using a Rayonet reactor equipped with 2540 Å lamps. After 6 hr 75% of the starting material had disappeared. The remainder consisted of 32% 3-neopentylthiophene and 68% 2-neopentylthiophene. The 3-neopentylthiophene was collected by preparative glpc (Carbowax 20M, 7 ft, 90°): nmr (C_3D_6O) δ 0.90 (s, 9, $(CH_3)_3C$), 2.53 [s, (broad), 2, CH_2] and 7.1–7.5 (m, 3, ring protons); uv (96% C_2H_5OH) λ_{max} 235 mμ (extinction not measured because of lack of material). The mass spectrum of the isolated photoproduct showed the same cracking pattern as that of 2-neopentylthiophene but with some variations in relative abundances. These data identify the photoproduct as 3-neopentylthiophene.

A dark tar formed during irradiation that, after removal of the solvent, became solid after standing for several days. This material was soluble in ether and acetone and had mp 70–80°. It resisted further characterization.

Irradiation of 2-*t*-butylthiophene was carried out with a total of 3.10 g (0.0221 mol) as a 10^{-2} *M* solution in ether using a Rayonet reactor equipped with 2540 Å lamps. After 7 hr 45% of the starting material had disappeared and the remainder consisted of 23% 3-*t*-butylthiophene and 77% 2-*t*-butylthiophene. The 3-*t*-butylthiophene was isolated by preparative glpc (Carbowax 20M, 8 ft, 132°) and was identified from its nmr spectrum in CCl_4.

Irradiation of 2,5-di-*t*-butylthiophene was carried out with 1.14 g (0.0058 mol) in 10^{-2} *M* ether solution using a Rayonet reactor equipped with 2540 Å lamps. The optimum irradiation time was 18 hr after which time 66% of the starting material had disappeared and the remainder consisted of 53% 2,4-di-*t*-butylthiophene and 47% 2,5-di-*t*-butylthiophene. The 2,4-di-*t*-butylthiophene was isolated by preparative glpc (Carbowax 20M, 8 ft, 140°) and was identified from its nmr spectrum in CCl_4.

Irradiation of 2,4-di-*t*-butylthiophene was done in a variety of solvents and with several different lamps. Usually after about 12 hr the solutions became slightly yellow and after 24 hr usually *ca.* 50% of the starting material had been destroyed. In no case were any detectable amounts of new products seen. Irradiations at 0° and 50° failed to give significantly different results.

Irradiation of 3-methyl, benzyl, neopentyl, and *t*-butylthiophenes led only to their destruction. No new products could be observed by glpc during the course of the irradiations.

Irradiation of 2,2′-dithienyl was carried out with 0.60 g (0.0036 mol) in 500 ml of ether using a Hanau Q-700 lamp. The reaction mixture was irradiated 6 hr and the lamp was cleaned of deposit after 3 hr. Glpc analysis (DEGS, 6 ft, 190°) indicated the mixture to consist of 2,2′-dithienyl (260 mg), 2,3′-dithienyl (100 mg), 3,3′-dithienyl (*ca.* 10–15 mg), and benzo[*b*]thiophene (*ca.* 5 mg). One minor compound of short retention time was not identified. The above products were isolated by preparative glpc (Carbowax 20M, 7 ft, 180°) and were identified from their uv and ir spectra.

Irradiation of 2,3′-dithienyl was carried out with 1.0 g (0.0060 mol) in 500 ml of benzene using a Hanau Q-700 lamp. Irradiation was carried out for 90 hr with cleaning every 24 hr (reactions proceeded slower in benzene owing to competitive light absorption). Glpc (DEGS, 6 ft, 190°) showed the reaction mixture to consist of 2,3′-dithienyl (100 mg), 3,3′-dithienyl (65 mg), benzo[*b*]thiophene (*ca.* 40 mg), and 2,2′-dithienyl (trace). The above compounds were isolated by preparative glpc (Carbowax 20M, 7 ft, 180°) and were identified from their uv and ir spectra.

Irradiation of 3,3′-dithienyl was carried out in various solvents with different lamps and at different concentrations but in no case could any isomeric compounds be detected. The only observable reaction was slow decomposition of the 3,3′-dithienyl.

Effect of conditions on the irradiation of 2,3′- and 3,3′-dithienyl was investigated. In general, irradiations in benzene solution using a low pressure Hg lamp went slower than in ether solution but the same products were formed. Irradiation of either 2,2′- or 2,3′-dithienyl at 3500 Å in benzene solution led to neither isomerization nor disappearance of starting material. Addition of benzophenone to these solutions under the same irradiation conditions led to very slow destruction of the dithienyls but no isomerization was observed; the benzophenone was unaffected. Both 2,2′- and 2,3′-dithienyls were unchanged when irradiated in acetone using a Pyrex filter. During some irradiations in ether solution using an S-81 lamp, considerable amounts of finely divided glass wool were added to increase the surface area; this seemed to neither help nor hinder isomerization.

(16) (a) P. Truitt, E. H. Holst, and G. Sammons, *J. Org. Chem.*, **22**, 1107 (1957). (b) W. Minnis, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, 520.

(17) The procedure described by Steinkopf[18] for the preparation of 2-benzylthiophene involving the zinc chloride catalyzed addition of benzyl alcohol to thiophene gives a 2:1 mixture of 2-benzyl and 3-benzylthiophenes as shown by glpc (Carbowax 20M, 6 ft, 175°). This problem seems not to have been appreciated by several more recent workers.[19a–c]

(18) W. Steinkopf and W. Hanske, *Justus Liebigs Ann. Chem.*, **541**, 238 (1939).

(19) (a) G. H. Jeffery, R. Parker, and A. I. Vogel, *J. Chem. Soc.*, 570 (1961); (b) J. J. G. Cadogan, D. H. Hey, and W. A. Sanderson, *ibid.*, 3205 (1960). (c) K. Takahashi, T. Sone, Y. Matsuki, and G. Hazato, *Bull. Chem. Soc. Jap.*, **36**, 108 (1963).

(20) H. Schecter and H. C. Barker, *J. Org. Chem.*, **21**, 1473 (1956).

(21) E. C. Kooyman and J. B. H. Kroon, *Recl. Trav. Chim. Pays-Bas*, **82**, 464 (1963).

(22) An alternative synthesis of *t*-butyl-2-thienyl ketone involving the exhaustive methylation of 2-acetylthiophene with methyl iodide in the presence of KOH gave poorer yields and required more strenuous conditions than those reported for an analogous reaction on acetophenone.[23]

(23) J. U. Nef, *Justus Liebigs Ann. Chem.*, **310**, 316 (1900).

(24) H. Wynberg and U. E. Wiersum, *J. Org. Chem.*, **30**, 1058 (1965).

Irradiation of 5,5′-dideuterio-2,2′-dithienyl was carried out with 3.93 g (0.0234 mol) in 3.6 l. of ether using a Hanau Q-700 lamp. The irradiation was carried out for 4–5 hr with 600 ml batches and the lamp was cleaned of deposit after 2 hr. The combined irradiation solutions consisting of *ca.* 27% 2,3′-isomer and 73% 2,2′ isomer plus traces of 3,3′-isomer and benzo[*b*]thiophene were filtered of solid deposit, were evaporated to dryness, and the solid residue was chromatographed over a short Al_2O_3 column using benzene as eluent. Preparative glpc (Carbowax 20M, 6 ft, 155°) was carried out allowing the isolation of 2,2′-dithienyl, 2,3′-dithienyl, and traces of benzo[*b*]thiophene and 3,3′-dithienyl (not enough for nmr spectra). The recovered 2,2′-isomer had nmr spectra in CCl_4 and C_3D_6O essentially identical with those of 5,5′-dideuterio-2,2′-dithienyl.[9] Within an accuracy limit of 5% neither deuterium scrambling nor deuterium loss took place. The recovered 2,3′-isomer (after subtracting peaks for 14% contamination of 2,2′-isomer) had nmr (C_3D_6O) δ 7.37 [d (deuterium broadened), 1, J = 1.2 Hz, 4′-H], 7.55 (d, 1, J = 1.2 Hz, 2′-H), 7.03 [d (deuterium broadened), 1, J = 3.6 Hz, 4-H], and 7.20 (d, 1, J = 3.6 Hz, 3-H); (CCl_4) 7.20 [m (poorly resolved), 2, 2′,4′-H], 6.89 [d (deuterium broadened), J = 3.8 Hz, 4 H], and 7.07 (d, 1, J = 3.8 Hz, 3 H). These data are consistent with the spectra expected for 5,5′-dideuterio-2,3′-dithienyl. Within the accuracy limits, integration ratios indicated no loss of deuterium.

Irradiation of 2,5′-dideuterio-2,3′-dithienyl was carried out with the same amounts and under the same conditions described for 5,5′-dideuterio-2,2′-dithienyl. The crude irradiation product, as determined by glpc (DEGS, 6 ft, 160°), consisted of 7% benzo[*b*]thiophene, 2% 2,2′-dithienyl, 79% 2,3′-dithienyl, and 12% 3,3′-dithienyl. Preparative glpc (Carbowax, 6 ft, 175°) allowed separation into the individual components. The recovered 2,3′-isomer was greater than 99% pure as estimated by glpc. Its nmr spectrum in both C_3D_6O and CCl_4 closely resembled those of the starting material. Some minor differences were noted, particularly in the region where absorption for the 3-substituted ring would be expected; no interpretation was possible, however. The recovered 3,3′-isomer was 7% contaminated with the 2,3′-isomer and had (after subtacting impurity absorptions) nmr (CCl_4) δ 7.22 (s, all protons); (C_3D_6O) 7.59 (d, 1.00, J = 1.4 Hz, 2-proton) and 7.43 [s (broad), 3.25, 3,4′,5′-protons]. Very weak absorptions were seen around the δ 7.59 doublet. These spectra are consistent with those expected for *ca.* 90% 2,5′-dideuterio-3,3′-dithienyl with *ca.* 10% unknown isomers.[9]

The recovered amount of 2,2′-isomer was not pure and consisted of *ca.* 60% 2,2′-isomer, 33% 2,3′-isomer, and 7% benzo[*b*]thiophene. After subtracting impurity peaks two sets of doublets, J = 3.6 Hz and J = 5.1 Hz, could (with imagination) be distinguished. This dubious assignment would indicate the presence of 3,5′-dideuterio-2,2′-dithienyl.

The isolated benzo[*b*]thiophene was >99% pure as estimated by glpc. The nmr (CCl_4) consisted of a series of peaks located between δ 7.48 and 7.12 from which two sets of doublets at δ 7.22 (J = 5.4 Hz) and 7.35 (J = 5.4 Hz) [reported[8] for 3 and 2 protons, J = 5.5 Hz at δ 7.22 and 7.35 respectively] could be resolved as well as a broad singlet at *ca.* δ 7.22 [reported[8] for 5 proton, 7.26 and 6-proton; 7.24]. In addition, a weak set of peaks ranging from δ 7.73 to 8.03 were present; assuming a total of 4 protons in the molecule these peaks accounted for less than one proton. This spectrum is consistent with that expected for 4,7-dideuteriobenzo[*b*]thiophene in which the 5,6-protons have collapsed to a singlet. Integration ratios indicate about *ca.* 80% this isomer plus *ca.* 20% unidentified isomer(s).

Irradiation of 2,2′-dideuterio-3,3′-dithienyl and 2,2′,5,5′-tetradeuterio-3,3′-dithienyl in 6.10^{-2} *M* ether solution led to considerable decomposition. The recovered compounds showed minor differences in their nmr spectra that were not readily interpretable.

Solvent effects on dithienyl irradiations were determined using a Rayonet reactor equipped with 2537 Å lamps. A quartz vessel with a screw type stirrer was used. Light intensities were determined by using *o*-nitrobenzaldehyde in alcohol solution as an actinometer;[25] ϵ quantum yield of 0.5 was taken for the isomerization to *o*-nitrobenzaldehyde acid. The average light intensity absorped by the contents of the flask was $1.7 \pm 0.1.10^{21}$ quanta/hr. The quantum yields for disappearance of 2,2′- and 2,3′-dithienyl in various solvents are summarized in Table I.

Registry No.—2-Methylthiophene, 554-14-3; 2-benzylthiophene, 13132-15-5; 2-neopentylthiophene, 4891-29-6; 2-*t*-butylthiophene, 1689-78-7; 2,5-di-*t*-butylthiophene, 1689-77-6; 2,2′-dithienyl, 492-97-7; 2,3′-dithienyl, 2404-89-9; 5,5′-dideuterio-2,2′-dithenyl, 18592-88-6; 2′,5-dideuterio-2,3′-dithienyl, 18592-89-7.

(25) P. A. Leighton and F. A. Lucy, *J. Chem. Phys.*, **2**, 756 (1934); J. N. Pitts, Jr., J. K. S. Wan, and E. A. Schuck, *J. Amer. Chem. Soc.*, **86**, 3606 (1964); R. M. Kellogg, M. B. Groen, and H. Wynberg, *J. Org. Chem.*, **32**, 3093 (1967).

Preparation and Reactions of Some Trifluorovinylcarbinols Containing Perhalomethyl Groups[1]

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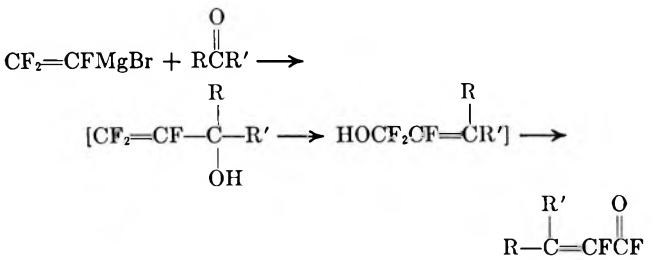
The reaction of trifluorovinyllithium with hexafluoro- and *syn*-dichlorotetrafluoroacetone and trifluoroacetyl chloride has given the corresponding tertiary alcohols. The trifluorovinyl carbinols are thermally stable and do not rearrange under acid or basic conditions; their acetates rearrange. They react with SF_4 and PCl_5 to give rearranged products. Methanol adds across the carbon–carbon double bond to give the corresponding ether.

Knunyants[2] and his associates have reported that the reaction of trifluorovinylmagnesium bromide with acetaldehyde, acetone, and benzaldehyde leads to α-fluoro-α,β-unsaturated acid fluorides; they postulated a mechanism for this reaction as follows.



Subsequent reports[3] from our laboratory have shown that these rearrangements usually occur during the purification step and that it is possible to trap the carbinol. Thus, the reaction product of trifluorovinyllithium and benzaldehyde when treated with 2-naphthyl isocyanate gave the corresponding urethan in 53% yield. Some carbinols can be isolated in the pure state and caused to rearrange in the presence of acids; trifluoromethylcyclohexanol has been found to fall into this category.

We now wish to report that the carbinols I and II

I

II

are extremely resistant to either thermal or acid-catalyzed rearrangement. When I and II were passed through a tube heated to 500°, they were recovered unchanged, and even when I was heated to 225° for 40 hr it was recovered unchanged. In addition to demonstrating that $CF_2{=}CFC(CF_3)_2OH$ does not rearrange as does $CF_2{=}CFC(CH_3)_2OH$, this latter experiment also shows that the compound does not dimerize, a reaction characteristic of many compounds containing the $CF_2{=}CF$ group. Similarly, no cyclobutane other than the dimer of $CF_2{=}CFCl$ was obtained when I was heated with $CF_2{=}CFCl$ for 18 hr at 175°; I was recovered quantitatively.

Attempts were made to cause the rearrangement of II by refluxing in 60% aqueous sulfuric for 36 hr and by subjection to 95% sulfuric acid for 2 weeks but only starting material was recovered. It might be presumed that, since the oxygen atom of the carbinol furnishes electrons to the difluoromethylene moiety of the trifluorovinyl group, rearrangement would be favored by converting the alcohol to its sodium salt. However, this was not the case since no reaction occurred when II was refluxed with 20% aqueous sodium hydroxide.

These unusual thermal stabilities and resistance to rearrangement led us to study other chemical properties of I and II.

These carbinols, along with $(CF_2{=}CF)_2C(OH)CF_3$ (III), were made by the reaction of trifluorovinyllithium with CF_2COCF_3, $CF_2ClCOCF_2Cl$, and CF_3COCl in yields of 75%, 65%, and 85%, respectively. Unsuccessful attempts were made to produce the trifluorovinyllithium reagent by the reaction of trifluoroethylene with butyllithium in hexane as ether, which is usually used, is difficult to remove. The failure of this proton exchange reaction suggests that the butyllithium hexamers which are known to exist in the commercial hydrocarbon solvents are too unreactive for this proton exchange and must be broken down by ether.

The acetates of I and II were prepared and were found to rearrange at 450° but not at 400°. The best synthetic route to the acetates was *via* the reaction of acetyl chloride with the unhydrolyzed lithium salts obtained from trifluorovinyllithium and the carbonyl compound. Using this procedure, the acetates of I and II were obtained in yields of 70% and 74%, respectively. The products from the rearrangement of the acetate of I were acetyl fluoride and perfluoro-2-methyl-2-butenoyl fluoride (50% yield). The acetate of II gave 4-chloro-3-(chlorodifluoromethyl)-2,4,4-trifluoro-2-butenoyl fluoride in 73% yield. The products from the pyrolyses were identified as acid fluorides from their infrared spectra and then converted to esters which were characterized by elemental analysis and ^{19}F nmr spectra. Presumably the reaction follows the mechanism postulated[4] for the rearrangement of $CF_2{=}CFC(OH)(CF_3)CH_3$ which gives 2-fluoro-3-trifluoromethyl-2-butenoyl fluoride.

Barna[5] has reported that phenyltrifluoromethylchlorodifluoromethyl carbinol reacts rapidly with alcoholic potassium hydroxide to give 2-phenyl-2,3,3,3-

(1) Presented at the 5th International Fluorine Symposium, Moscow, U. S. S. R., July 21–25, 1969.

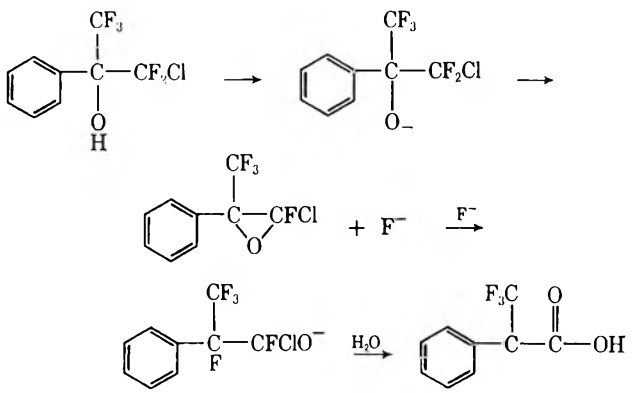
(2) R. N. Sterlin, R. D. Yatsenko, and I. L. Knunyants, *Khim Nauka Prom.*, **3**, 540 (1958); *Chem. Abstr.*, **53**, 4195 (1959).

(3) P. Tarrant, P. Johncock, and J. Savory, *J. Org. Chem.*, **28**, 839 (1963).

(4) F. G. Drakesmith, R. D. Richardson, O. J. Stewart, and P. Tarrant, *ibid.*, **33**, 286 (1968).

(5) P. M. Barna, *Aust. J. Chem.*, **21**, 1089 (1968).

tetrafluoropropionic acid quantitatively. He postulated the following mechanism.

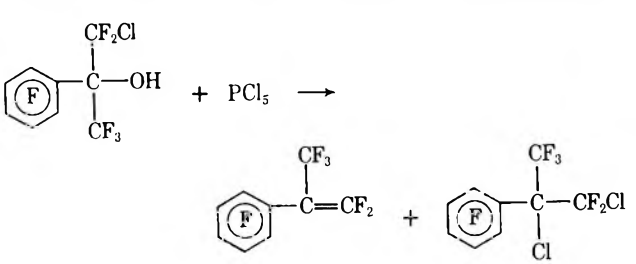


It was felt that II might undergo a similar rearrangement to CF_2=CF-CF(CF_2Cl)CO_2H. When the reaction was carried out an inseparable mixture of two compounds resulted. These were complex products which were not identified although the ^{19}F nmr spectrum was indicative of small ring compounds or compounds with a CHF group. On the basis of the reactions described below it appears more likely that the latter type of compound was obtained.

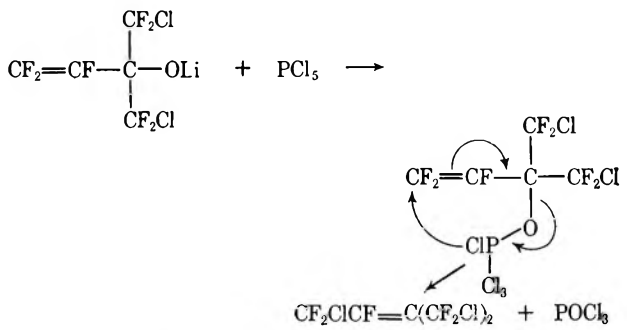
The reaction was repeated with CF_2=CFC(CF_3)$_2$OH, and the products were readily identified. Thus when I was refluxed for 24 hr with methanolic potassium hydroxide, a 13% yield of methyl 3-hydroxy-3-trifluoromethyl-2,4,4,4-tetrafluorobutanoate was formed. When heating was carried out for a shorter period, the alcohol adduct, 4-methoxy-3-trifluoromethyl-1,1,1,3,4,4-hexafluoro-2-butanol was obtained. Obviously this latter product is transformed to the former upon prolonged treatment with base. The products can be accounted for by the addition of alcohol across the double bond and subsequent reaction of the fluoro ethers to give the ester. The formation of ethers and esters from the reaction of alcohols and compounds containing the difluoromethylene group is well known.

1,3-Dichloropropanes, when treated with zinc, gives cyclopropanes. An experiment was carried out to determine if a small ring compound would be obtained from CF_2=CFC(CF_2Cl)$_2$OH; however, it appears difficult to effect cyclization as attempts to close the ring by the use of zinc in 2-propanol failed. The fact that the zinc reacted was shown by the formation of CF_2=CFC-(CF_2Cl)(CF_2H)OH in 44% yield. The ^1H nmr spectrum of this compound shows a broad singlet at τ 6.0 and a triplet at 3.84 (J = 57 cps), in a ratio of 1:1 indicative of the OH and isolated CF_2H group. Infrared, mass, and ^{19}F nmr spectra also confirmed the assigned structure.

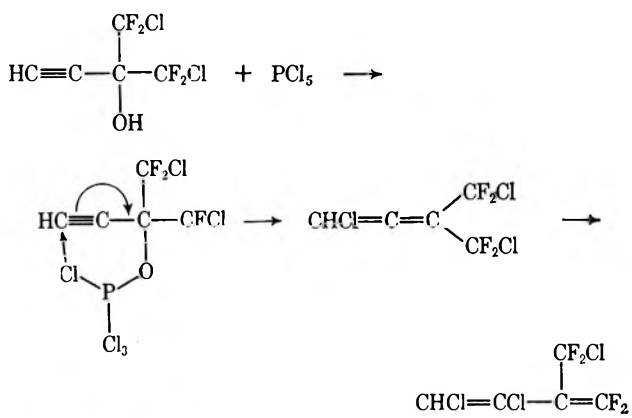
Kaufman and Braun[6] reported that phosphorus pentachloride reacts with 2-pentafluorophenyl-1,1,1,3,3-pentafluoro-3-chloro-2-propanol to give perfluoro-α-methylstyrene and its dichloride.



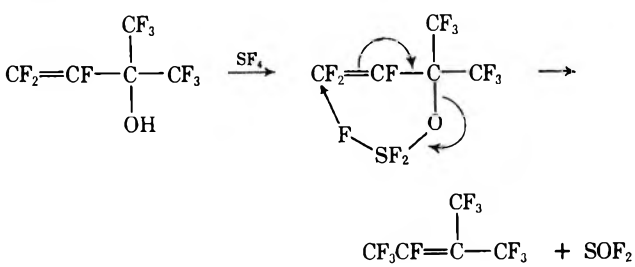
When II was treated with PCl_5 the reaction proceeded slowly, presumably because of the low nucleophilicity of the alcohol; however, the lithium salt of II reacted rapidly to give a rearranged product in 58% yield. Since the reaction of hydroxy compounds with PCl_5 is known to involve an intermediate phosphite ester, the following mechanism is postulated.



This result is similar to that reported by Dear and Gilbert[7] who found that HC≡C—C(CF_2Cl)$_2$OH gave a diene when treated with PCl_5 *via* the postulated allene intermediate.



The reaction of I and sulfur tetrafluoride gave perfluoro-2-methyl-2-butene, presumably by a cyclic intermediate as shown.



This type intermediate has been postulated for reactions of SF_4 with acetylenic alcohols containing CF_3 groups;[7] however, the reaction with I required much higher temperatures and longer reaction time.

Experimental Section[8]

Preparation of Trifluorovinyllithium in Hexane–Ether and Its Reaction with Hexafluoroacetone: The Preparation of 2-Trifluoromethylperfluoro-3-buten-2-ol (I).—In a 500-ml flask with

(6) M. H. Kaufman and J. P. Braun, *J. Org. Chem.*, **31**, 3090 (1966).

(7) R. E. A. Dear and E. E. Gilbert, *ibid.*, **33**, 819 (1968).

(8) Analyses were by Peninsular ChemResearch, Inc., Gainesville, Fla.

nitrogen sweep and magnetic stirrer, butyllithium (0.2 mol) in 130 ml of hexane and 40 ml of ether was cooled to −78° in a Dry Ice–acetone bath and trifluoroethylene (20 g, 0.25 mol) condensed into the solution. The reaction mixture was stirred for 2 hr and hexafluoroacetone (38 g, 0.23 mol), previously condensed in a cold trap, was distilled into the reaction mixture. The mixture was allowed to warm slowly to room temperature. (a) The reaction mixture was hydrolyzed with 20 ml of water and 20 ml of concentrated hydrochloric acid. The organic layer was separated, dried and distilled to give CF_2=$CFC(CF_3)_2OH$ (I), 24 g containing twenty per cent ether (40%), bp 80–85°. Ten grams of the crude product was dissolved in 50 ml of ten per cent sodium hydroxide. The solution was boiled for 5 min, cooled and acidified with concentrated hydrochloric acid. The alcohol layer was dried over Drierite and distilled to give 6 g of pure sample: bp 83–85°; $n^{24}D$ 1.3002. (Drake smith, *et. al.*,[4] reported bp 86°, $n^{24}D$ 1.3000.) (b) The reaction mixture was hydrolyzed with 40 ml of 15% sodium hydroxide. The aqueous layer was separated, acidified with hydrochloric acid and dried over Drierite. Distillation gave I, 27–32 g (54–65%), bp 80–85°, containing 5–10% ether. (c) The solvent from a duplicate of the above reaction was removed under an aspirator vacuum with a heat lamp. The residue was hydrolyzed with 25 ml of concentrated hydrochloric acid and the alcohol layer separated and dried. Distillation gave I, 35–37 g (71–75%), bp 83–85°, containing less than 5% ether.

1-Chloro-2-chlorodifluoromethyl-1,1,3,4,4-pentafluoro-3-buten-2-ol (II).—To the lithium reagent from butyllithium (0.2 mol) and trifluoroethylene (20 g, 0.25 mol) was added dropwise 1,3-dichlorotetrafluoroacetone (44 g, 0.22 mol) in 30 ml of ether, precooled in a dropping funnel containing Dry Ice–acetone mixture. The bright yellow solution was allowed to warm slowly. (a) The mixture was hydrolyzed with 20 ml of water and 20 ml of concentrated hydrochloric acid. The organic layer was separated, dried and distilled to give CF_2=$CFC(CF_2Cl)_2OH$, II, 28 g (50%) containing 15% ether, bp 118–123°. A sample of II was purified by preparative glpc to give pure II: bp 120°; $n^{23}D$ 1.3666; ir 2.95 (m), 5.65 (m) and 13.65 (s) μ; ^1H nmr broad singlet at τ 4.5; mass spectrum 280 (M) (2 Cl), 198 (M − CF_2Cl) (1 Cl), 85 (CF_2Cl), and 81 (CF_2=CF).

Anal. Calcd for $C_5HCl_2F_7O$: C, 21.43; H, 0.36. Found: C, 21.28; H, 0.51.

(b) The reaction mixture was then subjected to hydrolysis with 40 ml of 15% sodium hydroxide. The aqueous layer was separated and acidified with concentrated hydrochloric acid. The alcohol layer was separated and dried over Drierite. Distillation gave II, 32–36 g (57–65%), bp 118–122°, with 5–10% ether.

Perfluoro-3-methyl-1,4-pentadien-3-ol.—Trifluoroacetyl chloride (13.2 g, 0.1 mol) was added to a flask containing the lithium reagent from butyllithium (0.2 mol) and trifluoroethylene (0.2 mol) at −78°. The reaction mixture was allowed to warm slowly to room temperature. The solvent was removed under reduced pressure and the residue hydrolyzed with hydrochloric acid. The organic layer was separated, dried and distilled to give $(CF_2$=$CF)_2C(CF_3)OH$ (22 g, 85%): bp 91°; $n^{25}D$ 1.3351; ir 2.9 (m), 5.65 (vs), 7.55 (s), 7.95 (m), 8.3 (m), 8.8 (m), 9.35 (m), 10.6 (m) 11.19 (m), and 13.6 (m) μ; ^1H nmr spectrum had a broad singlet centered at τ 4.7; mass spectrum 260 (M), 241 (M − F), 191 (M − CF_3), and 69 (CF_3).

Anal. Calcd for C_6HF_9O: C, 27.69; H, 0.38. Found: C, 27.47; H, 0.52.

Attempted Reaction of II with Sulfuric Acid.—In a glass tube, II (3.0 g, 0.011 mol) was sealed with 95% sulfuric acid (0.5 g, 0.002 mol) and allowed to stand at room temperature for 2 weeks. The insoluble sulfuric acid was removed with a transfer pipet and the alcohol transferred to a trap under vacuum. No residue remained. No product other than II appeared on the glpc.

Attempted Reaction of II with Aqueous Sulfuric Acid.—Alcohol II (8.0 g, 0.029 mol) was refluxed with 20 ml of 60% aqueous sulfuric acid for 36 hr. The lower alcohol layer was separated and dried. Transfer of the alcohol under vacuum gave 7.6 g of recovered alcohol but no residue. No peak except II appeared in the glpc.

Reaction of II with Aqueous Sodium Hydroxide.—A solution of II (6.0 g, 0.022 mol) in 10 ml of 20% sodium hydroxide was refluxed for 18 hr. Acidification yielded II (5.2 g). No residue remained on vacuum transfer and no reaction product could be detected on the glpc.

Reaction of II with Zinc Dust in 2-Propanol.—Alcohol II (20 g, 0.07 mol) was added to a rapidly stirred mixture of zinc dust (17 g, 0.26 g-atom) in 20 ml of refluxing 2-propanol. The refluxing mixture was stirred for 72 hr. The flask was connected to a trap cooled in Dry Ice–acetone, evacuated, and the volatile liquid was transferred. The residue was poured into 75 ml of water and the lower layer was separated, dried over Drierite and distilled to give II (4.8 g) and 1-chloro-2-difluoromethyl-1,1,3,4,4-pentafluoro-3-buten-2-ol (IV), 6.2 g (44%): bp 73–75° (180 mm); $n^{32}D$ 1.3540; ir 2.8 (m), 3.0 (m), 3.32 (w) and 5.65 (s) μ; ^1H nmr triplet at τ 3.84 (J = 57 cps), broad singlet τ 6.0 with areas in the ratio 1:1; the ^{19}F nmr spectrum was consistent with this structure; mass spectrum peaks at 246 (M) (1 Cl), 195 (M − CF_2H) (1 Cl), and 161 (M − CF_2Cl).

Preparation of 2-Acetoxy-2-trifluoromethylperfluorobutene-3 (V).—(a) Alcohol I (18.6 g, 0.075 mol) was added to acetyl chloride (25 g, 0.32 mol) containing 2.0 g of sodium acetate and the mixture was refluxed for 72 hr. The reaction mixture was hydrolyzed with 50 ml of water, the organic layer separated and washed with 50 ml water, 50 ml of 10% sodium hydroxide solution, another 50 ml of water, and dried over $CaSO_4$. The basic extract was acidified to give 8 g of unreacted alcohol. The dried product was distilled to give V, 6.4 g (48%): bp 102–104°; $n^{24}D$ 1.3186; ^1H nmr sharp singlet at τ 7.92; ir 3.40 (m) and 5.67–7 (s) μ; mass spectrum base peak at 43 ($COCH_3$) and peaks at 290 (M), 231 (M − $COCH_3$), and 221 (M − CF_3).

Anal. Calcd for $C_7H_3F_9O_2$: C, 28.97; H, 1.04. Found: C, 29.11; H, 1.12.

(b) To lithium chips (1.2 g, 0.17 g-atom) in 50 ml of ether under an argon atmosphere I (12.4 g, 0.05 mol) was added. The reaction was left to stir under argon for 24 hr. Excess lithium was removed with tweezers, and acetyl chloride (10 g, 0.13 mol) was added slowly. The reaction mixture was stirred for 2 hr and worked up as in (a). No alcohol was recovered. Distillation yielded 11.3 g of acetate (78%). (c) To the lithium reagent from butyllithium (0.2 mol in 130 ml of hexane plus 40 ml of ether) and trifluoroethylene (20 g, 0.25 mol), hexafluoroacetone (0.33 g, 0.2 mol) was added. When the solution warmed to room temperature, the solvent was removed under reduced pressure (aspirator). Acetyl chloride (25 g, 0.32 mol) was added to the syrupy residue. The vigorous reaction was stirred for 4 hr and worked up as in (a). Distillation yielded 43 g (74%) of acetate. 74% yield.

Preparation of 2-Acetoxy-1-chloro-2-chlorodifluoromethyl-3,4,4-trifluoro-3-butene (VI).—(a) Alcohol II (20 g, 0.071 mol), sodium acetate (1 g), and acetyl chloride (25 g, 0.32 mol) were refluxed for 72 hr. The mixture was poured into ice water and the organic layer was separated, washed twice with 25 ml of 10% sodium hydroxide and dried over calcium chloride. Distillation gave CF_2=CF—$C(CF_2Cl)_2OAc$ (VI): 18.5 g (81%); bp 155–157°, $n^{22}D$ 1.3773; ir 3.35 (vs), 5.65 (m), and 5.70 (m) μ; ^1H nmr sharp singlet at τ 8.01; mass spectrum base peak at 43 ($COCH_3$) and 287 (M − Cl) (1 Cl), 263 (M − $COCH_3$) (2 Cl), and 273 (M − CF_2Cl).

Anal. Calcd for $C_7H_3Cl_2F_7O_2$: C, 26.00; H, 0.91; F, 41.28. Found: C, 25.86; H, 1.06; F, 41.44.

Reactions of Perfluorovinylcarbinols with Phosphorus Pentachloride.—Alcohol II (14.0 g, 0.05 mol) and phosphorus pentachloride (10.5 g, 0.05 mol) were refluxed for 24 hr with stirring. The reaction mixture was hydrolyzed by pouring it over 100 g of crushed ice. The organic layer was separated, washed with 25 ml of water, 40 ml of 15% sodium hydroxide solution, and 20 ml of water, and was dried over calcium chloride. The basic extract was acidified to give 5.5 g of II. Distillation of the product gave 1,4-dichloro-2-chlorodifluoromethyl-1,1,3,4,4-pentafluorobutene-2, (XIII), 6.2 g (58%): bp 112–113°; $n^{23}D$ 1.3676; ir 5.90 (m), 6.05 (m), 9.55 (vs), 10.01 (s), 11.7 (s), and 12.65 (s) μ; mass spectrum 298 (M) (3 Cl) 279 (M − F) (3 Cl), 263 (M − Cl) (2 Cl), 213 (M − CF_2Cl) (2 Cl) and no peak at 81 (CF_2=CF).

Anal. Calcd for $C_3Cl_2F_7$: C, 20.02. Found: C, 19.91.

Reaction of the Lithium Salt of I with Phosphorus Pentachloride.—Crude (90%) lithium salt of I from reaction of trifluorovinyl lithium with hexafluoroacetone (14 g, 0.85 mol) was placed in a 50-ml flask with phosphorus pentachloride (14 g, 0.07 mol). A vigorous reaction began immediately. The flask was connected to a trap cooled in Dry Ice–acetone. After the reaction subsided, the trap contained essentially pure 4-chloro-2-trifluoromethyl-1,1,1,3,4,4-hexafluorobutene-2, 4.4 g (33%): bp 53–55°; $n^{24}D$ <1.3000; ir 2.98 (s), 7.45 (s), 10.0 (s), 10.3 (s) and 12.1 (s) μ.

Anal. Calcd for C_5ClF_9: C, 22.51. Found: C, 22.21.

Thermal Reactions of Perfluorovinylcarbinols. Attempted Pyrolysis of I.—Alcohol I (6.0 g, 0.024 mol) was added dropwise under nitrogen to a glass-packed column heated to 550°. The

trap contained 5.5 g of brown liquid which showed only I on the glpc.

Attempted Pyrolysis of II.—Alcohol II (6.5 g, 0.023 mol) was added dropwise to the glass packed column under nitrogen heated to 475°. The yellow liquid recovered left an infinitessimal residue on removal of the volatile liquid which the glpc showed to be only II (6.1 g).

Attempted Dimerization of I.—Alcohol I (6.0 g, 0.024 mol) was sealed in a thick-walled glass tube and heated to 225° for 40 hr. The liquid remained colorless and showed no reaction products on the glpc. It left no residue on distillation and 5.9 g of I were recovered.

Pyrolysis of 2-Acetoxy-2-trifluoromethylperfluorobutene-2.—Acetate V (20.0 g, 0.69 mol) was pyrolyzed at 450°. After three passes 15.5 g of material were found in the two traps. Distillation gave a mixture of acetyl fluoride, 6.0 g, bp 20–60°; 5.5 g (43.8%) of perfluoro-3-methyl-2-butenoyl fluoride, VIII, bp 63–63°; and 4.7 g of residue (85% V by vpc). The two low boiling fractions were combined, added to 10 ml of absolute ethanol and allowed to stand overnight. The mixture was washed with 50 ml of water, 20 ml of 5% sodium hydroxide, and 15 ml of water. Drying over $CaCl_2$ and distillation gave 6.2 g of (44.3%) ethyl perfluoro-3-methyl-2-butenoate (X): bp 108°; $n^{23}D$ 1.3286; pmr of X showed a quartet at τ 5.47 (J = 7 cps) and (triplet τ 8.60 (J = 7 cps), the areas being in the ratio 2:3; ir 3.3–3.4 (m), 5.78 (s), 5.98 (s), 10.0 (s), 10.75 (s), 11.70 (s), 13.65 (s) and 14.71 (s) μ; mass spectrum 254 (M), 239 (M − CH_3), 209 (M − C_2H_2O) and 69 (CF_3).

Anal. Calcd for $C_7H_5F_7O_2$: C, 33.08; H, 1.97. Found: C, 33.32; H, 2.17.

Pyrolysis of 2-Acetoxy-1-chloro-2-chlorodifluoromethyl-3,4,4-trifluoro-3-butene (VI).—Acetate (VI) (30.0 g, 0.094 mol) was pyrolyzed at 550°. After one pass, conversion was approximately 90%. Distillation of material in the taps gave acetyl fluoride, 4.2 g (80%), and 4-chloro-3-chlorodifluoromethyl-2,4,5-trifluoro-2-butenoyl fluoride (IX), 16.5 g (73%): bp 95–97°, $n^{23}D$ 1.3650; ir 5.45 (m), 6.02 (m), 7.60 (s), 9.55 (s), and 11.5 (s) μ. For further characterization IX was converted to the ethyl ester. Compound IX (8,0 g, 0.031 mol) was dissolved in 20 ml of absolute ethanol and allowed to stand overnight. Distillation gave ethyl 4-chloro-3-chlorodifluoromethyl-2,4,4-trifluoro-2-butenoate (XI), 4.0 g (45%): bp 95–97° (85 mm); $n^{24}D$ 1.3911; ir 3.43 (w), 3.45 (w), 5.70 (s), and 6.00 (s) μ; pmr (quartet τ 5.72 J = 7 cps) and (triplet 8.65 J = 7 cps), with areas in the ratio 2:3.

Anal. Calcd for $C_7H_5Cl_2F_5O_2$: C, 29.27; H, 1.74. Found: C, 29.59; H, 1.78.

Reaction of I with Methanolic Potassium Hydroxide.—(a) In 20 ml of absolute methanol, I (10.0 g, 0.04 mol) was refluxed for 24 hr with potassium hydroxide (7.0 g, 0.1 mol). A gelatinous solid precipitated. The reaction mixture was acidified with 25 ml of concentrated hydrochloric acid and 20 ml of water, and the lower layer separated and dried. Separation on preparative glpc gave methyl 3-hydroxy-3-trifluoromethyl-2,4,4,4-tetrafluorobutanoate (XV), 1.4 g (13.5%): bp 160°; $n^{24}D$ 1.3416; ir 2.9 (vs), 3.34 (m), 5.8 (s), 6.2 (m), 10.45 (vs) and 14.3 (vs) μ; pmr doublet at τ 4.78 (J = 46 cps), broad singlet at τ 5 and a sharp singlet at τ 6.00; ^{19}F nmr spectrum was consistent with this structure; mass spectrum base peak at 59 (CH_3OCO) and peaks at 239 (M − F), 227 [M − CH_3O], 199 (M − CH_3OCO), and 189 (M − CF_3).

Anal. Calcd for $C_6H_5F_7O_3$: C, 27.91; H, 1.94. Found: C, 28.39; H, 2.21.

(b) In 20 ml of absolute methanol, compound I (10.0 g, 0.04 mol) was refluxed for 18 hr with potassium hydroxide (7 g, 0.1 mol). The mixture was acidified with gaseous hydrogen chloride and the methanol distilled off. Purification on preparative glpc gave 4-methoxy-2-trifluoromethyl-1,1,1,3,4,4-hexafluoro-2-butanol (XVI), 2.2 g (19%): bp 76° (100 mm); $n^{24}D$ 1.1316; ir 2.82 (s), 3.32 (m), 14.0 (vs), and 14.65 (vs) μ; pmr had a doublet at τ 5.32 ($J_{H-\alpha F}$ = 45 cps, $J_{H-\beta F}$ = 11 cps) a broad singlet at τ 6.07 and a sharp singlet at τ 6.52 in the ratio 1:1:3; ^{19}F nmr spectrum was consistent with this structure; mass spectum had a base peak at 81 (CH_3OCF_2) and peaks at 261 (M − F) and 191 (M − F–CF_3).

Anal. Calcd for $C_6H_5F_9O_2$: C, 25.61; H, 1.79. Found: C, 25.75; H, 1.79.

Reaction of the Lithium Salt of I with Potassium Methoxide in Methanol.—Potassium metal (8.0 g, 0.2 mol) was dissolved in 50 ml of absolute methanol under nitrogen and crude lithium salt of I (25 g, 0.1 mol) (from the reaction trifluorovinyllithium and hexafluoroacetone) was added. A vigorous reaction began immediately and the refluxing solution was left to stir for 12 hr. Acidification with 95% sulfuric acid, and distillation gave XVI, 6.5 g (25%), and 11 g of a mixture of XV with a third product inseparable by glpc or distillation.

Reaction of II with Potassium Hydroxide in Methanol.—In 40 ml of absolute methanol, II (20.0 g, 0.071 mol) and potassium hydroxide (14 g, 0.2 mol) were refluxed for 6 hr. Potassium fluoride (4.9 g, 0.081 mol) precipitated. The solution was acidified with gaseous hydrogen chloride. Addition of 20 ml of water gave a lower layer which when dried and distilled gave a liquid, 5.5 g: bp 100–102° (mm) (this was a mixture of two compounds or isomers inseparable by glpc); pmr spectrum showed a complex group of peaks between τ 5.0 and 6.5; the ^{19}F nmr spectrum suggested the presence of a small ring or a CFH group; ir spectrum 2.91 (s), 3.36 (m), 2.91 (s), 3.36 (m), 5.8 (s), 10.0 (s), and 13.45 (s) μ; mass spectrum with an ionizing voltage of 10 eV had peaks at 207, 209, 292, 293, 294, and 295.

Registry No.—I, 15052-92-3; II, 25055-22-5; $(CF_2{=}CF)_2C(CF_3)OH$, 25055-23-6; IV, 25055-24-7; V, 25055-25-8; VI, 25080-61-9; VIII, 24499-79-4; IX, 25055-27-0; X, 24449-44-3; XI, 25055-29-2; XIII, 25055-30-5; XV, 25055-31-6; XVI, 25055-32-7; 4-chloro-2-trifluoromethyl-1,1,1,3,4,4-hexafluorobutene-2, 25055-33-8.

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Electronic Effects in Elimination Reactions. VI. Bimolecular Eliminations from 1-Aryl-2-propyl and 2-Aryl-1-propyl Tosylates and Bromides[1]

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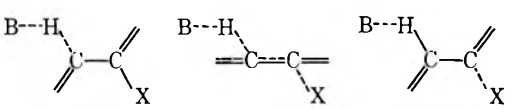
A kinetic study of the bimolecular, base-promoted elimination reactions of the α- and β-methyl-substituted β-phenylethyl tosylates and bromides is reported. The reactions were conducted in potassium *t*-butoxide in *t*-butyl alcohol and sodium ethoxide in ethanol. These compounds are shown to develop less carbanion character in the transition states of their elimination reactions than in those of β-phenylethyl tosylates and bromides. The ρ values and *t*-butoxide:ethoxide rate ratios show that the decrease in carbanion character is greatest for reactions of the α-methyl compounds.

The flexibility of the structure of bimolecular elimination transition states is well documented.[5] Between the extreme anionic, E1cB, and cationic E1 eliminations reside the bimolecular concerted E2 processes whose transition states vary across a mechanism spectrum as shown schematically below. The position of a transition state on this spectrum is determined by the relative amounts of C–H and C–X bond breaking and C–C double-bond character. These in turn are dependent upon the nature of the leaving group, X, the base, B, the substituents on the molecule, the base strength, and the solvent medium.[5c]



Extensive mechanistic studies of E2 reactions have been conducted on β-phenylethyl compounds using as leaving groups halides, *p*-toluenesulfonate (tosylate), dimethyl sulfide, and trimethylamine.[6,7] The overall effect of a 2-aryl substituent is to shift the mechanism toward one of more carbanion character but with the retention of a single, concerted transition state. The degree of carbanion character, as shown by Hammett σ–ρ correlations, increases as the leaving group becomes more electronegative and as β-hydrogen acidity increases. Kinetic isotope effects for both the proton[8a] and various leaving groups,[8b,c] and rate studies in D_2O[9] have complemented these earlier findings for β-phenylethyl compounds.

There have been fewer investigations of substituted β-phenylethyl compounds. The deuterium kinetic isotope effect for elimination of 1-phenyl-2-methyl-2-chloropropane in methoxide–methanol has been measured,[10] and the low value of k_H/k_D has been postulated to reflect the small amount of C–H bond breaking in the transition state. On the other hand, k_H/k_D determined by Shiner and Smith[11] for 2-phenyl-1-bromopropane in sodium ethoxide–ethanol is larger than the theoretical maximum value,[12] and it has been proposed that the high value is a result of quantum-mechanical tunneling.

In this paper we report on rates, solvent effects, and Hammett correlations of a variety of methyl-substituted β-phenylethyl compounds. Our intention was to determine to what extent such substitution would be reflected in detectable and predictable changes in transition state structure, and to give added tests to several different methods for measuring subtle changes in mechanism.

Results and Discussion

In earlier studies[13] we have shown that *trans*-2-phenylcyclopentyl tosylate undergoes a remarkably rapid, bimolecular *syn* elimination reaction in *t*-butoxide–*t*-butyl alcohol solution. Making use of Hammett σ–ρ relationships, we proposed that coplanar *syn* eliminations were in general more E1cB-like than coplanar *anti* eliminations. In drawing these conclusions we used the extensive work on elimination from β-phenylethyl compounds as a standard. The cyclic systems studied, however, were necessarily alkylated β-phenylethyl systems, and few studies of the effect of alkyl substituents on E2 eliminations have been reported. We therefore decided to see how important such substituents are in controlling transition state geometry in acyclic E2 reactions. In Tables I–IV the rates of E2 reaction of β-phenylethyl tosylates and bromides substituted with an α- or a β-methyl group are reported for both *t*-butoxide–*t*-butyl alcohol and ethoxide–ethanol solution. In Table V Hammett correlations and activation parameters are reported, and in

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(2) University of Colorado.

(3) Taken in part from the Ph.D. theses of D. L. Storm, Iowa State University, 1966, and J. T. Frey, Iowa State University, 1964.

(4) National Science Foundation Summer Research Participant, 1966; National Institutes of Health Predoctoral Fellow, 1966–1968. Taken in part from the Ph.D. thesis of C. G. Naylor, University of Colorado, 1968.

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TABLE I

RATE CONSTANTS FOR ELIMINATION FROM 1-ARYL-2-PROPYL TOSYLATES AND BROMIDES, Y-$C_6H_4CH_2CH(CH_3)$-X, IN POTASSIUM *t*-BUTOXIDE–*t*-BUTYL ALCOHOL SOLUTION

X	Y	Temp, °C	$k_{E2} \times 10^4$[a] l. mol^{-1} sec^{-1}	1-Aryl-1-propene[b] yield, %
OTs	H	50.0	9.32 ± 0.10[c]	98
OTs	H	30.0	2.39 ± 0.03	
OTs	*p*-Cl	50.0	21.8 ± 0.2	
OTs	*m*-Br	50.0	52.0 ± 0.8	97
OTs	*p*-CH_3	50.0	4.56 ± 0.11	98
OTs	*p*-OCH_3	50.0	2.74 ± 0.04	
Br	H	50.0	94.1 ± 1.0	
Br	*p*-Cl	50.0	177. ± 3	
Br	*m*-Br	50.00	274. ± 6	97
Br	*p*-CH_3	50.0	45.5 ± 0.9	100
OTs	β-Phenylethyl	50.00	110[d]	100
Br	β-Phenylethyl	50.00	369[d]	100

[a] Determined spectrophotometrically. [b] Determined by gas chromatography. The 1-aryl-1-propenes were approximately 5% *cis* and 95% *trans*. The remaining product was 3-aryl-1-propene. [c] Average deviation from the mean of two or more runs. [d] Reference 6b.

TABLE II

RATE CONSTANTS FOR ELIMINATION FROM 1-ARYL-2-PROPYL TOSYLATES AND BROMIDES, Y-$C_6H_4CH_2CH(CH_3)$-X, IN SODIUM ETHOXIDE–ETHANOL SOLUTION

X	Y	Temp, °C	$k_{E2} \times 10^4$[a] l. mol^{-1} sec^{-1}	1-Aryl-1-propene yield, %[b]
OTs	H	50.0	3.42 ± 0.09[c]	81
OTs	H	30.0	0.42 ± 0.02	
OTs	*p*-Cl	50.0	9.85 ± 0.26	
OTs	*p*-Cl	30.0	1.08 ± 0.04	
OTs	*m*-Br	50.0	16.4 ± 0.4	93
OTs	*p*-CH_3	50.0	2.87 ± 0.06	80
OTs	*p*-OCH_3	50.0	2.32 ± 0.10	
OTs	*p*-OCH_3	30.0	0.28 ± 0.01	
Br	H	50.0	19.2 ± 0.4	
Br	H	30.0	2.55 ± 0.04	
Br	*p*-Cl	50.0	85.4 ± 2.0	
Br	*m*-Br	50.0	155. ± 5	97
Br	*m*-Br	30.0	20.9 ± 0.6	
Br	*p*-CH_3	50.0	17.7 ± 0.05	99
OTs	β-Phenylethyl	50.0	5.98[d]	100
Br	β-Phenylethyl	50.0	34.2[d]	100

[a] Determined spectrophotometrically. [b] Determined by gas chromatography. 3-Aryl-1-propene and ethyl ether were the other products. The 1-aryl-1-propenes were approximately 90% *trans* and 10% *cis*. [c] Average deviation from the mean of two or more runs. [d] Reference 6b.

Table VI some of these data are compared with literature values for related compounds.

Looking first at the data for elimination in *t*-butoxide, we see that substitution of β-phenylethyl by either an α- or a β-methyl group decreases the E2 rate for both tosylates and bromides. For the α-CH_3 group the decrease is a factor of 6 and 2, respectively,[14] and for the β-CH_3 group the decrease is a factor of 25 and 5. These rate decreases are most likely due to an inductive

(14) The β-phenylethyl rates must be divided by two to give rates per hydrogen atom, since *trans* olefin is the nearly exclusive product from 1-phenyl-2-propyl tosylate and bromide.

TABLE III

RATE CONSTANTS FOR ELIMINATIONS FROM 2-ARYL-1-PROPYL TOSYLATES AND BROMIDES, Y-$C_6H_4CZ(CH_3)CH_2$-X, IN POTASSIUM *t*-BUTOXIDE–*t*-BUTYL ALCOHOL SOLUTION

X	Y	Z	Temp, °C	$k_{E2} \times 10^4$[a] l. mol^{-1} sec^{-1}	Olefin[b] yield, %
OTs	*p*-H	H	49.8	2.14 ± 0.03[c]	92
OTs	*p*-H	H	29.8	0.34 ± 0.01	93
OTs	*p*-Cl	H	49.8	7.06 ± 0.10	100
OTs	*m*-Br	H	49.8	17.80 ± 0.50	96
OTs	*m*-Br	D	49.8	2.83 ± 0.12	90
OTs	*p*-CH_3	H	49.8	0.93 ± 0.01	90
OTs	*p*-CH_3	D	49.8	0.15 ± 0.01	64
OTs	*p*-OCH_3	H	49.8	0.66 ± 0.01	80
Br	*p*-H	H	49.8	41.10 ± 1.00	100
Br	*p*-H	H	29.8	8.19 ± 0.18	100
Br	*p*-Cl	H	49.8	118.00 ± 3.00	100
Br	*m*-Br	H	49.8	201.00 ± 4.00	98
Br	*m*-Br	D	49.8	26.40 ± 0.10	100
Br	*p*-CH_3	H	49.8	21.10 ± 0.50	100
Br	*p*-CH_3	D	49.8	3.19 ± 0.01	99
Br	*p*-OCH_3	H	49.80	14.70 ± 0.70	96

[a] Determined titrimetrically. [b] Determined spectrophotometrically. [c] Average deviation from the mean of two or more runs.

effect of the methyl, although steric effects may also play a role.[15]

In ethoxide–ethanol the rate effect of a methyl group is more interesting. We have pointed out previously[13] that a shift from *t*-butoxide–*t*-butyl alcohol to ethoxide–ethanol has the effect of moving the transition state in the E1 direction, since the base strength decreases and the ionizing power of the medium increases. Attachment of a β-methyl group still decreases the rate (by a factor of 5 for the tosylate and 1.2 for the bromide) but attachment of an α-methyl group increases the E2 rate slightly in both cases. These results are at least consistent with the view that the greater ionizing power of the ethanol can, in the case of secondary but not primary tosylates and bromides, overcome the inductive effect of a methyl group.

For the tosylates, Hammett correlations and rate ratios in *t*-butoxide–ethoxide, as summarized in Table VI, also show a consistent pattern. In all cases the ρ value is larger in the stronger base, less ionizing solvent. From the ρ values alone one would say that substitution of an alkyl group moves the transition state in the E1 direction, and the *t*-butoxide:ethoxide rate ratios support this conclusion, although the latter effects could also be accounted for by involving steric effects.

The rate ratios and ρ values among the bromides (Table VI) do not show such a perfect correspondence, but the general trend is correct. The usefulness of the solvent rate ratio is perhaps increased if one notes that the tertiary bromide, $C_6H_5CH_2C(CH_3)_2Br$ reacts 7 times *faster* in ethoxide–ethanol than it does in *t*-butoxide–*t*-butyl alcohol.[16] The ρ values for the bromides in Table VI are greater in the less basic, better solvating medium ethoxide–ethanol than in *t*-butoxide–*t*-butyl alcohol. This trend is opposite to that expected on the basis of medium effects[5] and that observed among the tosylates. This anomaly is perhaps best explained by the greater ability of bromide, relative to tosylate, to

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Table IV

Rate Constants for Eliminations from 2-Aryl-1-propyl Tosylates and Bromides, Y-$C_6H_4CZ(CH_3)CH_2$-X, in Sodium Ethoxide–Ethanol Solution

X	Y	Z	Temp, °C	$k_{E2} \times 10^4$[a] l. mol^{-1} sec^{-1}	Olefin[b] yield, %
OTs	*p*-H	H	49.8	0.56 ± 0.02[c]	64
OTs	*p*-H	H	29.8	0.054 ± 0.002	71
OTs	*p*-Cl	H	49.8	1.35 ± 0.01	64
OTs	*m*-Br	H	49.8	2.64 ± 0.02	75
OTs	*m*-Br	D	49.8	0.56 ± 0.04	44
OTs	*p*-CH_3	H	49.8	0.27 ± 0.01	41
OTs	*p*-CH_3	D	49.8	0.066 ± 0.001	15
OTs	*p*-OCH_3	H	49.8	0.28 ± 0.01	28
Br	*p*-H	H	49.8	14.50 ± 0.50	100
Br	*p*-H	H	29.8	1.58 ± 0.02	100
Br	*p*-Cl	H	49.8	58.00 ± 0.10	97
Br	*m*-Br	H	49.8	112.00 ± 1.00	100
Br	*m*-Br	D	49.8	15.90 ± 0.1	95
Br	*p*-CH_3	H	49.8	9.34 ± 0.47	100
Br	*p*-CH_3	H	49.8	1.47 ± 0.01	94
Br	*p*-OCH_3	D	49.8	8.32 ± 0.06	100

[a] Determined titrimetrically. [b] Determined spectrophotometrically. [c] Average deviation from the mean of two or more runs.

Table V

Hammett Correlations and Enthalpies and Entropies of Activation for Eliminations from β-Phenylethyl-X Compounds

Compound	X	Base–solvent	ρ,[a] at 50°	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} deg^{-1}
α-CH_3	OTs	*t*-BuOK–*t*-BuOH	1.88 ± 0.03	12.6	−33
α-CH_3	OTs	EtONa–EtOH	1.33 ± 0.07	19.7	−13
α-CH_3	Br	*t*-BuOK–*t*-BuOH	1.37 ± 0.03		
α-CH_3	Br	EtONa–EtOH	1.84 ± 0.11	19.0	−12
β-CH_3	OTs	*t*-BuOK–*t*-BuOH	2.18 ± 0.03	17.2	−22
β-CH_3	OTs	EtONa–EtOH	1.81 ± 0.02[b]	22.0	−9
β-CH_3	Br	*t*-BuOK–*t*-BuOH	1.75 ± 0.02	15.0	−23
β-CH_3	Br	EtONa–EtOH	2.06 ± 0.05[b]	20.9	−6

[a] Calculated by the method of least squares. [b] Omitting *p*-methoxy.

Table VI

Hammett Correlations and *t*-Butoxide–Ethoxide Rate Ratios for Eliminations from 2-Phenyl-Substituted Tosylates at 50°

Compound	ρ (*t*-BuOK–*t*-BuOH)	ρ (EtONa–EtOH)	$\frac{k_{E2}\ (t\text{-BuOK})}{k_{E2}\ (\text{EtONa})}$
	Tosylates		
2-Phenylethyl	3.39[a,b]	2.27[a,b]	22.0
2-Phenyl-1-propyl	2.18	1.81	3.9
1-Phenyl-2-propyl	1.88	1.32	2.7
cis-2-Phenylcyclopentyl	1.48[c]	0.99[c]	1.2
	Bromides		
2-Phenylethyl	2.08[a,b]	2.14	11.0
2-Phenyl-1-propyl	1.75	2.06	2.8
1-Phenyl-2-propyl	1.37	1.84	5.0

[a] From ref 6b. [b] Measured at 30°. [c] From ref 13c.

disperse the incipient negative charge at the benzyl carbon in poorly solvating *t*-butyl alcohol by allowing more double-bond formation in the transition state.[6b]

Experimental Section[17]

Arylacetones.—The arylacetones were prepared from the corresponding arylacetic acids and methyllithium.[18] A 0.9 *M* solution of methyllithium in anhydrous ether was added slowly to a stirred solution of the arylacetic acid in anhydrous ether during a period of 2 hr. The reaction was stirred at room temperature for 12 hr. After addition of water and extraction with ether the organic solution was washed with water and dried, and the solvent was removed. Distillation of the residue gave 70–80% yield of the arylacetone. Phenylacetone had bp 120–122° (30 mm), lit.[19] 109–112° (24 mm); *p*-chlorophenylacetone had bp 163–165° (20 mm), lit.[20] 80–85° (0.4 mm); *m*-bromophenylacetone had bp 95–97° (0.2 mm); *p*-methylphenylacetone had bp 70–71°, lit.[21] 92–94° (3.0 mm); and *p*-methoxyphenylacetone had bp 147–148° (22 mm), lit.[22] 92–94° (3.0 mm).

1-Aryl-2-propanols.—These alcohols were prepared by lithium aluminum hydride reduction of the corresponding arylacetones. A solution of 0.09 mol of the arylacetone in 100 ml of anhydrous ether was added dropwise to a stirred solution of 0.06 mol of lithium aluminum hydride in 50 ml of anhydrous ether. The reaction was stirred for 5 hr at room temperature and quenched by addition of wet ether. After acidification and extraction with ether, the organic layer was dried and the solvent removed. The residue was distilled to give about 90% yield of the 1-aryl-2-propanol. 1-Phenyl-2-propanol had bp 127–128° (15 mm), lit.[23] 92° (2.0 mm); 1-(*p*-chlorophenyl)-2-propanol had bp 94–95° (0.1 mm); 1-(*p*-methylphenyl)-2-propanol had bp 66–67° (0.4 mm), lit.[20] 97° (2 mm); and 1-(*p*-methoxyphenyl)-2-propanol had bp 158–161° (15 mm), lit.[23] 121° (3 mm).

2-Arylpropenes.—α-Methylstyrene was purchased from Aldrich Chemical. The remaining 2-arylpropenes were prepared by dehydration of the corresponding 2-aryl-2-propanols.[24] The

(17) Melting and boiling points are uncorrected. Analyses were performed by Dr. A. Bernhardt of the Max-Planck Institute and Spang Microanalytical Laboratory, Ann Arbor, Mich. Ultraviolet spectra were determined on Cary Model 14 and Beckman DK-2A spectrophotometers.

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(21) T. I. Temnikova and V. I. Vekslei, *Zh. Obshch. Khim.*, **19**, 171 (1947).

(22) A. Buzas and C. Dufor, *Bull. Soc. Chim. Fr.*, 139 (1950).

(23) V. R. Likkterov and V. S. Etlis, *Zh. Obshch. Khim.*, **27**, 2867 (1957).

(24) "Organic Reactions," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 204.

alcohol, 0.1–1.0 mol, was dripped slowly into a flask heated at 220° containing a powdered mixture of 6.0 g of potassium acid sulfate, 0.05 g of catechol, and 0.05 g of picric acid. Water and the 2-arylpropene were removed from the flask as they were formed by distillation at 50 mm through a 10-cm, glass-bead fractionating column. The distillate was extracted with ether, and the ether solution was dried and evaporated. The 2-arylpropenes were purified by distillation and obtained in 61–77% yield. 2-*p*-Chlorophenylpropene had bp 43–45° (1.5 mm), lit.[25] 78–80° (8 mm); 2-*m*-bromophenylpropene had bp 54–56° (0.8 mm), lit.[25] 68–72° (2 mm); 2-*p*-methylphenylpropene had bp 48–49° (3.5 mm), lit.[26] 76–78° (19 mm); and 2-*p*-methoxyphenylpropene had bp 61–62° (1.4 mm), lit.[25] 63–66° (0.5 mm).

2-Aryl-1-propanols.—These alcohols were prepared by hydroboration of the corresponding 2-arylpropenes using a modification of Brown's procedure.[27] A solution of 0.17 mol of the 2-arylpropene and 0.13 mol of sodium borohydride in 75 ml of bis(2-ethoxyethyl) ether was cooled to 0° under a nitrogen atmosphere. To this stirred solution was slowly added 0.17 mol of boron trifluoride etherate. The reaction was stirred at room temperature for 1 hr followed by the careful addition of 50 ml of 6 *M* sodium hydroxide at 0°. With continued cooling 50 ml of 30% hydrogen peroxide was added dropwise and the reaction was stirred for 1 hr at room temperature. The reaction was worked up in the usual way, and the 2-aryl-1-propanols were purified by distillation to give 85–98% yields. 2-Phenyl-1-propanol had bp 94–96° (3.5 mm); 2-(*p*-chlorophenyl)-1-propanol had bp 109–112° (0.3 mm); 2-(*m*-bromophenyl)-1-propanol had bp 92° (0.4 mm); 2-(*p*-methylphenyl)-1-propanol had bp 80° (0.4 mm), lit.[28] 102° (5 mm); and 2-(*p*-methoxyphenyl)-1-propanol had bp 95° (0.5 mm), lit.[29] 80° (0.15 mm).

2-Deuterio-2-aryl-1-propanols.—These were prepared by a modification of Sondheimer's procedure.[30] 2-Deuterio-2-(*m*-bromophenyl)-1-propanol had bp 103–106° (0.3 mm) and 2-deuterio-2-(*p*-methylphenyl)-1-propanol had bp 86–90° (0.3 mm). Their nmr spectra indicated that they were greater than 95% deuterated in the 2-position.

***p*-Toluenesulfonates.**—These were prepared by Tipson's procedure,[31] purified by crystallization from ether–pentane, and dried *in vacuo*.

1-Phenyl-2-propyl *p*-toluenesulfonate had mp 93.5–95°. *Anal.* Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; S, 11.07. Found: C, 66.14; H, 6.14; S, 10.91.

1-(*p*-Chlorophenyl)-2-propyl *p*-toluenesulfonate had mp 79.5–80.5°. *Anal.* Calcd for $C_{16}H_{17}ClO_3S$: C, 59.16; H, 5.28; Cl, 10.92; S, 9.87. Found: C, 59.25; H, 5.31; Cl, 11.00; S, 9.99.

1-(*p*-Bromophenyl)-2-propyl *p*-toluenesulfonate had mp 57–58°. *Anal.* Calcd for $C_{16}H_{17}BrO_3S$: C, 52.04; H, 4.64; Br, 21.64; S, 8.68. Found: C, 52.08; H, 4.63; Br, 21.62; S, 8.81.

1-(*p*-Methylphenyl)-2-propyl *p*-toluenesulfonate had mp 49–50°. *Anal.* Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62; S, 10.53. Found: C, 67.17; H, 6.69; S, 10.49.

1-(*p*-Methoxyphenyl)-2-propyl *p*-toluenesulfonate had mp 77–78°. *Anal.* Calcd for $C_{17}H_{20}O_4S$: C, 63.73; H, 6.29; S, 10.01. Found: C, 63.76; H, 6.39; S, 10.01.

2-Phenyl-1-propyl *p*-toluenesulfonate had mp 50–50.5°. *Anal.* Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; S, 11.07. Found: C, 66.33; H, 6.10; S, 11.21.

2-(*p*-Chlorophenyl)-1-propyl *p*-toluenesulfonate had mp 64.5–65°. *Anal.* Calcd for $C_{16}H_{17}ClO_3S$: C, 59.16; H, 5.28; S, 9.87. Found: C, 59.46; H, 5.46; S, 10.06.

2-(*m*-Bromophenyl)-1-propyl *p*-toluenesulfonate had mp 60.5–61°. *Anal.* Calcd for $C_{16}H_{17}BrO_3S$: C, 52.04; H, 4.64; S, 8.68. Found: C, 52.22; H, 4.77; S, 8.80.

2-Deuterio-2-(*m*-bromophenyl)-1-propyl *p*-toluenesulfonate had mp 62–63°.

2-(*p*-Methylphenyl)-1-propyl *p*-toluenesulfonate had mp 42.5–43°. *Anal.* Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62; S, 10.53. Found: C, 67.35; H, 6.71; S, 10.72.

2-Deuterio-2-(*p*-methylphenyl)-1-propyl *p*-toluenesulfonate had mp 39–40°.

2-(*p*-Methoxyphenyl)-1-propanol *p*-toluenesulfonate had mp 37–39°, lit.[29] 34–35°. *Anal.* Calcd for $C_{17}H_{20}O_4S$: C, 63.73; H, 6.29; S, 10.01. Found: C, 63.55; H, 6.23; S, 9.93.

Bromides.—These compounds were prepared by treating the corresponding *p*-toluenesulfonates with lithium bromide in acetone solution. A solution of 0.02 mol of the *p*-toluenesulfonate and 0.06 mol of anhydrous lithium bromide in 40 ml of anhydrous acetone was stirred at room temperature for 3 days. The resulting inhomogeneous mixture was poured into 100 ml of water and extracted with ether. The ether solution was dried and evaporated. The residual bromide was purified by distillation and obtained in yields of 85–95%. 1-Phenyl-2-bromopropane had bp 46–47° (0.1 mm); 1-(*p*-chlorophenyl)-2-bromopropane had bp 80–81° (0.5 mm); 1-(*m*-bromophenyl)-2-bromopropane had bp 90–91° (0.5 mm); 1-(*p*-methylphenyl)-2-bromopropane had bp 63–64° (0.3 mm); 2-phenyl-1-bromopropane had bp 50–54° (0.2 mm); 2-(*p*-chlorophenyl)-1-bromopropane had bp 72–74° (0.3 mm); 2-(*m*-bromophenyl)-1-bromopropane had bp 85–86° (0.3 mm); 2-deuterio-2-(*m*-bromophenyl)-1-bromopropane had bp 90–91° (0.8 mm); 2-(*p*-methylphenyl)-1-bromopropane had bp 55–57° (0.2 mm); 2-deuterio-2-(*p*-methylphenyl)-1-bromopropane had bp 69–70° (0.5 mm); 2-(*p*-methoxyphenyl)-1-bromopropane had bp 82–83° (0.3 mm); 2-phenyl-1-bromo-3-butene had bp 55–56° (0.9 mm).

Anhydrous Ethanol.—Absolute ethanol was refluxed with sodium and diethyl phthalate and distilled according to the method of Manske[32] to remove residual water.

Anhydrous *t*-Butyl Alcohol.—Commercial *t*-butyl alcohol (Eastman Kodak White Label) was fractionally distilled, a sharp center fraction boiling 82–82.5° (630 mm) being taken. This sample was then distilled twice from sodium.

Potassium.—Potassium metal was purified by repeated fusion in heptane. The lighter impurities floated to the surface and were skimmed off.

Second-Order Elimination Reactions.—A solution 0.02–0.06 *M* in base was prepared according to the following procedure. The bromide or *p*-toluenesulfonate (0.002–0.006 mol) was weighed into a 100-ml volumetric flask. It was dissolved in the desired amount of alcohol at room temperature and diluted to 100 ml with 0.2–0.3 *M* base solution. After shaking thoroughly 10-ml aliquots of the solution were pipetted at room temperature into 20-ml Pyrex ampoules which were then immediately immersed in ice–water and sealed. The solution in the ampoules was then equilibrated to reaction temperature.

The kinetics were measured by breaking open an ampoule, quenching the contents in ice-cold ethanol and titrating the unreacted base with standard hydrochloric acid.

For the faster elimination reactions ($k_2 > 10^{-2}$) the kinetics were measured directly from the 100-ml flask. In these cases the solution of substrate in alcohol was equilibrated to reaction temperature and then diluted to 100 ml with base solution which had also been equilibrated to reaction temperature. The solution was thoroughly shaken and requilibrated. The kinetics were measured by withdrawing 10-ml aliquots from the solution, quenching, and titrating.

Reaction rates measured using the two different methods agreed within 5%.

Substrate concentrations were determined accurately by measuring the zero and infinity point base concentrations.

The rates were calculated from each experimental point using the integrated form of the second-order rate equation. All necessary thermal expansion corrections were used. The rates were all cleanly second order.

The yields of olefins were determined by measuring the ultraviolet absorption of the last aliquot after the proper amount of dilution in 95% ethanol.

Pseudo-First-Order Elimination Reactions.—A solution approximately 0.01 *M* in the desired substrate and 0.1 *M* in the base was prepared by adding the base solution, equilibrated at the reaction temperature, to an accurately weighed sample of the substrate in 50-ml volumetric flask. The flask was immersed immediately in the constant-temperature bath and periodically shaken until the substrate had all dissolved.

Aliquots (5 ml) were then withdrawn at appropriate intervals and quenched by draining into ice-cold 95% ethanol. These solutions were immediately diluted to the proper concentrations for ultraviolet analysis.

(25) D. Seymour and K. B. Wolfstirn, *J. Amer. Chem. Soc.*, **70**, 1177 (1948).

(26) G. B. Bachman and H. M. Hellman, *ibid.*, **70**, 1772 (1948).

(27) H. C. Brown and G. Zweifel, *ibid.*, **82**, 4708 (1960).

(28) S. Muckherjee, *J. Indian Chem. Soc.*, **24**, 341 (1947).

(29) S. Winstein and A. H. Fainberg, *J. Amer. Chem. Soc.*, **80**, 459 (1958).

(30) W. Wolfe, M. Nussin, Y. Mazeir, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959); F. Sondheimer and M. Nussin, *ibid.*, **26**, 630 (1961).

(31) R. S. Tipson, *ibid.*, **9**, 235 (1944).

(32) R. H. Manske, *J. Amer. Chem. Soc.*, **53**, 1106 (1931).

All the reactions were carried out under pseudo-first-order conditions and the rate constants were calculated by the use of the equation

$$k_1 = \frac{2.303}{t} \log \frac{A_\infty - A_0}{A_\infty - A_t}$$

wherein A_∞ is the measured infinity absorption, A_0 is the absorbance at $t = 0$, and A_t is the absorbance at time t. Second-order rate constants were obtained by dividing the first-order rate constant by the base concentration.

The reported rate constants from both the titrimetric and spectrophotometric runs were calculated on an IBM 7044 computer using the method of least squares. In most cases duplicate runs were measured.

Ultraviolet Spectra of 1-Aryl-1-propenes and 2-Arylpropenes.—Molar extinction coefficients measured in 95% ethanol were the following: 1-phenyl-1-propene, 18,600 (248 mμ); 1-(4-chlorophenyl)-1-propene, 24,500 (255 mμ); 1-(3-bromophenyl)-1-propene, 20,900 (253 mμ); 1-(4-methoxyphenyl)-1-propene, 22,400 (258 mμ); 2-phenylpropene, 11,400 (243 mμ); 2-(4-chlorophenyl)propane, 15,700 (248 mμ); 2-(3-bromophenyl)-propene, 10,700 (245 mμ); 2-(4-methylphenyl)propene, 13,700 (248 mμ); and 2-(4-methoxyphenyl)propene, 16,200 (257 mμ).

Registry No.—Table I (X = OTs, Y = H), 14135-71-8; Table I (X = OTs, *p*-Cl), 23430-31-1; Table I (X = OTs, *m*-Br), 23430-32-2; Table I (X = OTs, *p*-CH_3), 23430-33-3; Table I (X = OTs, *p*-OCH_3), 898-95-3; Table I (X = Br, H), 2114-39-8; Table I (X = Br, *p*-Cl), 23430-36-6; Table I (X = Br, *m*-Br), 23430-37-7; Table I (X = Br, *p*-CH_3), 2114-40-1; Table I (X = OTs, β-phenylethyl), 4455-09-8; Table I (X = Br, β-phenylethyl), 103-63-9; Table III (X = OTs, Y = *p*-H, Z = H), 23430-41-3; Table III (X = OTs, *p*-Cl, H), 23465-00-1; Table III (X = OTs, *m*-Br, H), 23430-42-4; Table III (X = OTs, *m*-Br, D), 23430-43-5; Table III (X = OTs, *p*-CH_3, H), 23430-44-6; Table III (X = OTs, *p*-CH_3, D), 23430-45-7; Table III (X = OTs, *p*-OCH_3, H), 23430-46-8; Table III (X = Br, H, H), 1459-00-3; Table III X = Br, *p*-Cl, H), 23430-48-0; Table III (X = Br, *m*-Br, H), 23430-49-1; Table III (X = Br, *m*-Br, D), 23430-50-4; Table III (X = Br, *p*-CH_3, A), 23430-51-5; Table III (X = Br, *p*-CH_3, D), 23430-52-6; Table III (X = Br, *p*-OCH_3, H), 23430-53-7.

Electronic Effects in Elimination Reactions. VII. *syn* and *anti* Eliminations of the 3-Phenyl-2-norbornyl Tosylates[1]

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The four isomeric 3-phenyl-2-norbornyl *p*-toluenesulfonates were subjected to elimination in order to study the effect of geometry on the rate. The relative rates in potassium *t*-butoxide–*t*-butyl alcohol at 50° for the four modes of elimination are *exo–syn* (*exo*-β hydrogen–*syn* elimination)/*exo–anti*/*endo–syn*/*endo–anti* = 100:3.1:0.12:0.21. The rate differences are ascribed to a combination of dihedral angle, *endo*-hydrogen removal, and *endo* leaving group effects. The Hammett ρ values for *exo–syn* and *exo–anti* are both much larger than that for an *anti*-coplanar elimination. These results imply that *syn* elimination has an inherently greater demand for carbanion character than *anti* elimination, and that noncoplanar geometry increases the electronic requirements of *anti* elimination.

The usually preferred stereochemistry for bimolecular elimination is an *anti*-coplanar relationship between the acidic hydrogen and the leaving group,[5] but *syn* pathways have been shown to compete effectively with *anti* elimination in certain rigid cyclic systems,[6] and occasionally in flexible cyclic and acyclic systems.[7] It was theorized[6] that the rate of elimination is maximized as the dihedral angle between leaving group and acidic hydrogen approaches 180° (*anti* coplanar) and 0° (*syn* coplanar). Hine[8] has given a semitheoretical justification for this concept based on the "principle of least motion" involving a mechanical model of the E2 transition state. A quantum mechanical argument has been presented by Eliel, *et al.*,[9] to show that *syn*-coplanar elimination should be less favorable than *anti*-coplanar elimination, aside from all other factors such as steric and electrostatic repulsions.

The present study of 3-phenyl-2-norbornyl tosylates is an extension of earlier work[6] on the mechanisms of *syn* and *anti* eliminations of the 2-phenylcyclopentyl tosylates, which gave the first direct comparison of electronic requirements for *syn* and *anti* eliminations in a β-phenylethyl system. The norbornyl system has the advantage of a better defined geometry in which the dihedral angles are accurately known. Cyclopentyl derivatives are more flexible, so the ground-state geometry is not necessarily the same as that for the elimination transition state.

Results

The preparation of the four isomeric 3-phenyl-2-norbornyl tosylates was recently reported by Kleinfelter.[10] The same synthetic route to *endo*-3-phenyl-

(1) Part VI: C. H. DePuy, D. L. Storm, J. T. Frey, and C. G. Naylor, *J. Org. Chem.*, **35**, 2746 (1970). This work was supported in part by the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is made to the donors of said funds.

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(3) NSF Summer Research Participant, 1966; NIH Predoctoral Fellow, 1966–1968. Taken in part from the Ph.D. thesis of C. G. N., University of Colorado, 1968.

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(9) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 483.

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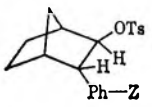
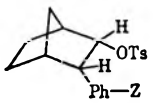
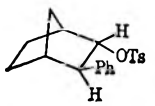
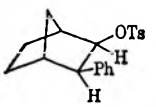
TABLE I

ELIMINATION RATE DATA FOR 3-ARYL-2-NORBORNYL TOSYLATES AT 50°

	Compound	Z	t-BuOK–t-BuOH	% elimination	k_{E2} × 10⁴ (l. mol⁻¹ sec⁻¹) EtONa–EtOH	% elimn
			exo–syn			
A		H	15.70 ± 1.50[a]	100		
		H	2.34 ± 0.05 (30°)	100		
		p-CH_3	7.06 ± 0.42	100		
		p-Cl	83.7 ± 0.4	100	1.45	48
		m-Cl	255 ± 12	100	2.37	74
			exo–anti			
B		H	0.482 ± 0.017	92	0.088 ± 0.005	62
		p-CH_3	0.185 ± 0.004	68		
		p-Cl	1.82 ± 0.23	100[b]		
		m-Cl	3.69 ± 0.15	100		
C			*endo–syn*			
			0.0195 ± 0.0005	94 ± 4		
D			*endo–anti*			
			0.0335 ± 0.0020	55 ± 3 (Base = 0.400 *M*)		
			0.0334 ± 0.0032	79 ± 2 (Base = 0.915 *M*)		

[a] Average deviation from the mean of two or more runs. [b] Assumed.

exo-2-norbornanol was used in the present work; oxidation of this alcohol to the corresponding ketone was achieved with dimethyl sulfoxide and dicyclohexylcarbodiimides.[11] This procedure yielded an epimeric mixture of 3-phenylnorbornanones, which was then reduced to a mixture of isomeric alcohols. This mixture was partially separable by crystallization and chromatography. (A sample of the least plentiful isomer, *exo*-3-phenyl-*exo*-2-norbornanol, was kindly supplied by Professor Kleinfelter.)

In Table I are given the measured second-order rate constants of the four isomeric tosylates. Included are data for phenyl-substituted tosylates of isomers A and B.

These tosylates gave good second-order kinetics and 100% elimination in most cases in *t*-butoxide–*t*-butyl alcohol. Because of the small quantities of isomers C and D available and their very slow rates, the rate constants are more uncertain. Percentages of elimination were calculated from ultraviolet absorbance infinity values and the measured extinction coefficients of the arylnorbornenes. Although the infinity samples did not discolor, polymerization of the 2-arylnorbornene products was possible because of the long time required for completion of the reactions. Thus the reported percentages are best regarded as minimum values.

Tosylate D gave the same k_{E2} but a higher olefin yield with higher base concentration. This is evidence for competition from a first-order ionization reaction. Simple calculations based on known data suggest that D can undergo processes other than 1,2 elimination. Nickon[12] measured the solvolysis rate of *exo*-norbornyl tosylate in *t*-butyl alcohol at 60° ($k_1 = 1.3 \times 10^{-5}$ sec^{-1}) while Kleinfelter[13] solvolyzed isomer D and *exo*-norbornyl tosylate in acetic acid. Assuming the *exo*-phenyl group decreases the solvolysis rate by the same factor in *t*-butyl alcohol as in acetic acid (128), a first-order rate constant for the solvolysis of D in *t*-butyl alcohol can be estimated ($k_1 = 1 \times 10^{-7}$ sec^{-1} at 60°, $\sim 0.5 \times 10^{-7}$ at 50°). The pseudo-first-order rate constant for D at 50°, 0.40 *M* *t*-butoxide, is 12.6×10^{-7} sec^{-1}. Therefore about 4% of the substrate is estimated to be reacting by an E1–SN1 pathway (2% at 0.915 *M* base), assuming all the olefin product arises from an E2 reaction. Second-order 1,3 elimination is also probably occurring.[12] Until product analyses and more accurate kinetic data are gathered, little more can be said about the non-E2 processes.

endo-Norbornyl tosylates solvolyze much more slowly than *exo*-tosylates;[13] so isomers B and C do not undergo E1–SN1 processes during elimination, but they are subject to 1,3 elimination and direct displacement reactions.[12] Vpc analysis of the reaction mixture of B revealed a product of shorter retention time than 2-phenylnorbornene which is assumed to be phenylnortricyclene. No peak of longer retention time was observed, so apparently no ether was formed. The few per cent nonolefin product from C was not identified.

Table II compares the phenylnorbornyl elimination data with those of 2-phenylcyclopentyl[6] and 2-phenylcyclobutyl[14] tosylates. Included are ρ values calculated from the data in Table I.

Discussion

If the cyclopentane ring were planar, the dihedral angle for *trans*-2-phenylcyclopentyl tosylate would be 0° and that for the *cis* isomer would be 120°. However, eclipsing effects force the ring out of planarity;[15] so that the two dihedral angles being considered are greater than 0° and 120°. Thus *syn* elimination is rendered less favorable, while the *anti* pathway becomes more favorable. Models suggest that the *cis* isomer can

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(12) A. Nickon and N. H. Werstiuk, *ibid.*, **89**, 3915 (1967).

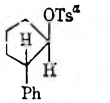
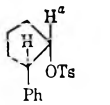
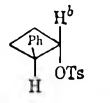
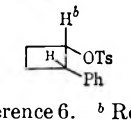
(13) D. C. Kleinfelter, E. S. Trent, J. E. Mallory, and T. E. Dye, *ibid.*, **88**, 5350 (1966).

(14) C. H. DePuy and C. H. Hendrickson, unpublished work.

(15) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 200.

Table II

syn:*anti* Rate Ratios and ρ Values at 50°

Compound	Mode	*syn*:*anti*	*t*-BuOK–*t*-BuOH	ρ	EtONa–EtOH	ρ
A	*exo–syn*		15.7	3.12 ± 0.05	1.0[c]	2.1[c]
		30.7				
B	*exo–anti*		0.482	2.56 ± 0.01	0.087	
C	*endo–syn*		0.0195			
		0.58				
D	*endo–anti*		0.0334			
	*syn*		2.9	2.76		
		0.10				
	*anti*		29.1	1.48	24.2	0.99
	*syn*		5.10	2.90		
		0.39				
	*anti*		13.0	2.18	1.16	1.26

[a] Reference 6. [b] Reference 14. [c] Calculated from a plot of two points.

achieve a dihedral angle approaching 180° with little strain. In fact *cis*-2-phenylcyclopentyl tosylate, with low ρ values and high rates in the two base–solvent media used, appears to exhibit behavior normal for an α,β-dialkyl-β-phenylethyl tosylate,[1] which presumably would undergo *anti*-coplanar elimination and show E1-like behavior.

Cyclobutane is puckered 25–30° out of planarity;[16] so dihedral angles are close to 30° and 150° for *cis* and *trans* substituents, respectively. That these angles are closer to 0° and 120° than those in cyclopentane is reflected in the larger *syn*:*anti* rate ratio. The *syn* rate is faster than that in the cyclopentyl system even though a more highly strained olefin is being formed. and the *anti* rate is slower.

The norbornane ring system is more rigid than the cyclobutyl or cyclopentyl system, so that the dihedral angles between hydrogen and leaving groups should be very close to 0° and 120° for *syn* and *anti* elimination, respectively. Torsional effects may prevent exact eclipsing, but the deviation is expected to be small. We, therefore, felt that in isomer A we would have very nearly the best possible model for a *syn* elimination, and in isomer B a similarly good example of a noncoplanar *anti* elimination. By comparing isomer C and D where these angles are equally well determined, with A and B we hoped to be able to separate various steric factors from conformational effects. In this we were only partly successful.

The elimination rates from isomers A and B were fully in accord with predictions made on the basis of the earlier hypotheses.[6] In the first place the *endo*-phenyl *exo*-tosylate (A) undergoes a bimolecular *syn* elimination with *t*-butoxide–*t*-butyl alcohol 30 times more rapidly than its isomer *endo*-phenyl *endo*-tosylate (B) undergoes *anti* elimination under the same conditions. This is by far the largest *syn*:*anti* ratio observed in the β-phenylethyl tosylate system, the corresponding ratio in the cyclopentyl compounds being 0.10.[17] In accordance with predictions we see that the change in ratio from 0.10 to 30 is due to a combination of two factors, a fivefold *increase* in the rate of *syn* elimination, and a 60-fold *decrease* in the rate of *anti* elimination. These changes are in the expected order if, in the norbornyl system, the *syn* elimination is more coplanar and the *anti* elimination is less coplanar, the latter being rigidly constrained to a 120° geometry. Acceleration of elimination due to *endo*-steric interactions in compound B is obviously not a significant factor.

The Hammett ρ values are also in accord with expectations (Table II). We have shown previously[6] that *syn* eliminations are more E1cB-like than *anti* eliminations; their ρ values are relatively high. So, too, ρ for *syn* elimination from the norbornyl tosylates is high. More enlightening is the high ρ value for *anti* elimination from the norbornyl compounds. If we examine a series of compounds 2-aryl-cyclopentyl tosylate, 2-aryl-cyclobutyl tosylate, and *endo*-2-aryl-*endo*-norbornyl tosylate in which the attainment of an *anti*-coplanar transition state becomes progressively more difficult, we find a steady increase in the ρ value for *anti* elimination, the values being 1.48, 2.18, and 2.56, respectively. Presumably these results indicate that, as the *anti* elimination deviates from exact coplanarity, more carbanionic character is needed in the transition state to drive off the leaving group. However, the rate of *anti* elimination is much less sensitive to deviations from coplanarity than is the rate of *syn* elimination.

Our studies of the *endo–syn* and *endo–anti* eliminations (compounds C and D) were hampered by synthetic difficulties, and by the much lower rates of elimination of the compounds, which allowed other reactions pathways to compete. Both *syn* and *anti* rates dropped, probably reflecting the lesser accessibility of

(16) J. D. Roberts and M. C. Caserio, "Modern Organic Chemistry," W. A. Benjamin Inc., New York, N. Y., 1967, p 91.

(17) It should be recalled that the corresponding ratio in the cyclohexyl system is <0.0001, presumably because a boat form would be required for a coplanar *syn* elimination.[6]

the *endo* hydrogen, but the *syn* rate dropped more than the *anti* rate. Nevertheless, the *syn*:*anti* ratio (0.6) is larger than that for any tosylate system so far investigated with the exception of the *exo* eliminations in this same system.

Ordinarily it is not possible to observe *syn* eliminations of tosylates in sodium ethoxide-ethanol solution. Since *syn* eliminations are E1cB-like, their rates are decreased by the use of a weak base like ethoxide, and the polar medium promotes competing solvolysis reactions. Because of the rapidity of *exo*–*syn* elimination, however, we were able to observe *syn* E2 eliminations in activated aryl systems. We have pointed out previously[6] the possible mechanistic significance of *t*-BuO^-:EtO^- rate ratios. For this *syn* elimination this ratio is 50–100, while for the corresponding *exo*–*anti* elimination it is only 5, and in coplanar *anti* eliminations it can be considerably less than 1.

The data gathered by LeBel[18] on the elimination reactions of 2,3-dihalonorbornenes show qualitatively the same dependence of relative rate on dihedral angle and proton accessibility. LeBel concluded that the mechanisms are concerted and E1cB-like. The present results, by allowing quantitative comparisons with other cyclic and noncyclic β-phenylethyl systems, strengthen and extend these conclusions.

Experimental Section

Melting points and boiling points are uncorrected. Vapor phase chromatographic analyses were performed on an Aerograph 200 or an F & M 700 instrument. Nmr spectra were measured on a Varian A-60 or A 60A spectrometer; chemical shifts are reported in parts per million from internal standard tetramethylsilane in δ units. Spectra descriptions are as follows: peak multiplicity—s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); peak areas—*n* (*n* protons). Ultraviolet spectra were measured on a Beckman model DK-2A or Coleman–Hitachi 124 spectrometer. Elemental analyses were performed by the Weiler and Strauss Analytical Laboratory, Oxford, England, Dr. A. Bernhardt of the Max-Planck-Institute, Mülheim, Germany, and Huffmann Laboratories, Wheatridge, Colo.

Preparation and Purification of Materials. Preparation of 2-Phenylbicyclo[2.2.1]heptyl Compounds. 2-Arylnorbornenes.—To an ether solution of phenyllithium prepared from 5.0 g (0.72 g-atom) of lithium and 93.0 g (0.592 mol) of bromobenzene was added an ether solution of 50.0 g (0.454 mol) of 2-norbornanone (Aldrich Chemical Co.) at a rate sufficient to maintain gentle reflux. The solution was allowed to stir for 2 hr and water was added slowly to remove excess phenyllithium and hydrolyze the salts. The aqueous phase was separated and extracted three times with portions of fresh ether. The combined ether solutions were dried over $MgSO_4$ and most of the ether was removed by atmospheric distillation. Approximately 0.1 g of *p*-toluenesulfonic acid was added and the contents of the flask were heated vigorously to promote dehydration. The water formed in the dehydration was removed by azeotropic distillation with benzene and the residue was distilled to yield 56.4 g (0.331 mol) of olefin, bp 79–81° (0.7 mm), lit.[19] bp 124–128° (17 mm) 73% yield. Vpc analysis showed the olefin to be about 98% pure, the remainder being a peak of shorter retention time, presumably phenylnortricyclene.

The *p*-methylphenyl compound was made by the same procedure using *p*-bromotoluene. The *m*-chlorophenyl and *p*-chlorophenyl compounds were made by the same procedure using Grignard reagents: 2-*p*-methylphenylnorbornene, bp 89–90° (0.3 mm), 73.4% yield; 2-*m*-chlorophenylnorbornene, bp 99–100° (0.45 mm), 78.3% yield; 2-*p*-chlorophenylnorbornene, bp 106–110° (0.9 mm), mp 55–57°, 73% yield.

endo-3-Aryl-*exo*-2-norbornanols.—2-Phenylbicyclo[2.2.1]hept-2-ene, 27.0 g (0.159 mol), and sodium borohydride, 3.2 g (0.085 mol), were dissolved in 150 ml of diglyme. To this solution of 13.0 g (0.092 mol) of boron trifluoride etherate in 40 ml of diglyme was added over a period of 1 hr. The solution was chilled in an ice bath and stirred for 2 additional hr. Water (20 ml) was added cautiously, followed by 40 ml of 3 *M* sodium hydroxide and 40 ml of 30% hydrogen peroxide solution. This mixture was stirred for 1 hr and was then poured into ice–water. The organic material was extracted with ether and the ether solution was dried and distilled to yield 21.8 g of alcohol, bp 111–113° (0.7 mm), 73% yield. Nmr analysis indicated that the hydroxyl group was exclusively in the *exo* position: *endo*-3-*p*-methylphenyl-*exo*-2-norbornanol, bp 130–133° (0.7 mm), mp 81.5–82°, 77% yield; *endo*-3-*m*-chlorophenyl-*exo*-2-norbornanol, bp 153–159° (0.9 mm), mp 75.5–76°, 66% yield; *endo*-3-*p*-chlorophenyl-*exo*-2-norbornanol, bp 124–129° (0.5 mm), 55% yield.

3-Phenyl-2-norbornanone.—To dimethyl sulfoxide (100 ml, distilled from calcium hydride under aspirator pressure) in a dry flask was added 14 g of 100% phosphoric acid and 31.2 g of 3-phenyl-2-norbornal in 100 ml of dry ether. When dicyclohexylcarbodiimide (100 g, Aldrich Chemical Co.) in 50 ml of ether was added, a precipitate began forming and the mixture became warm. After stirring 6 hr the solution was filtered to remove the dicyclohexylurea. To the filtrate was added 25 g of oxalic acid in 70 ml of methanol, and the mixture was again filtered. The solution was washed with aqueous sodium bicarbonate and water, then dried. Solvent removal and vacuum distillation gave 25 g of the ketone (75%): nmr[20] δ 1.3–1.9 (m, 6), 2.5–2.9 (2 m, 2), 3.32 (d, 1), 7.2 (s, 5). *endo*-3 H appears at 2.93 in epimerized ketone mixture.

In the same manner the three phenyl-substituted ketones were prepared: 3-(*p*-methylphenyl)-2-norbornanone, bp 120–130° (0.4 mm); nmr δ 1.1–2.0 (m, 6), 2.23 (s, 3), 2.4–2.8 (m, 2), 2.88 (d, 0.4), 3.25 (d, 0.6), 7.0 (s, 4). The two fractional peaks represent the *endo* and *exo* epimeric benzylic protons, respectively. 3-(*p*-Chlorophenyl)-2-norbornanone had mp 65–66°; nmr δ 1.3–2.2 (m, 6), 2.6–3.0 (2 m, 2), 3.33 (d, 1), 7.2 (s, 4). 3-(*m*-Chlorophenyl)-2-norbornanone had nmr δ 1.0–2.0 (m, 6), 2.3–3.0 (m, 2), 3.25 (d, 1), 7.1 (m, 4). *endo*-3-Phenyl-*endo*-2-norbornanol was obtained from the ketone by lithium aluminum hydride reduction in the manner previously described. Crystallization from petroleum ether gave alcohol with mp 69–70° (lit.[21] 71°); nmr δ 1.2–2.1 (m, 7), 2.4 (broad s, 2), 3.0 (q, 1), 7.25 (s, 5).

exo-3-Phenyl-*endo*-2-norbornanol.—The mother liquor above contained three isomeric alcohols by vpc analysis (Carbowax 20 M column at 210°) as well as some ketone and 2-phenylnorbornene. Dry column chromatography over alumina (Alcoa, type F-20) using petroleum ether with increasing amounts of ether eluted the components in the following order: 2-phenylnorbornene, 3-phenyl-2-norbornenone, di-*endo*- and di-*exo*-3-phenyl-2-norbornanol, and *exo*-3-phenyl-*endo*-2-norbornanol. The two *cis* isomers could not be separated. The last isomer was converted into its tosylate without further purification or analysis.

endo-3-(*p*-Methylphenyl)-*endo*-2-norbornanol was obtained from the ketone as described above: mp 109–109.5°; nmr δ 0.9–1.9 (m, 7), 1.9–2.2 (2 m, 2), 2.24 (s, 3), 2.84 (2 d, 1), 4.06 (2 d, 1), 7.0 (s, 4).

endo-3-(*p*-Chlorophenyl)-*endo*-2-norbornanol and *endo*-3-(*m*-chlorophenyl)-*endo*-2-norbornanol were obtained from their corresponding ketones as described above. One major product was obtained in each case, indicating that the ketones were only slightly epimerized: nmr of *p*-chloro alcohol, δ 1.2–2.0 (m, 7), 2.4 (broad s, 2), 3.0 (2 d, 1), 4.25 (2 d, 1), 7.2 (s, 4); nmr of *m*-chloro alcohol, δ 0.9–1.8 (m, 7), 2.3 (broad s, 1), 2.84 (broad s, 1.5), 3.0 (d, 0.5), 4.3 (2 d, 1), 7.2 (m, 4).

Tosylates.—The tosylate esters of the arylnorbornanols were prepared by the method of Tipson.[22] Nmr data below include only the chemical shifts and multiplicity of the 3- and 2-hydrogens, respectively.

endo-3-(X-Phenyl)-*exo*-2-norbornanol Tosylates.—The compound with X = H had mp 86–86.5° (reported 94–95°),[13] nmr δ

(18) N. A. LeBel, P. D. Beirne, E. R. Karger, J. C. Powers, and P. M. Subramanian, *J. Amer. Chem. Soc.*, **85**, 3199 (1963); N. A. LeBel, P. D. Beirne, and P. M. Subramanian, *ibid.*, **86**, 4144 (1964).

(19) D. C. Kleinfelter and P. von R. Schleyer, *J. Org. Chem.*, **26**, 3740 (1961).

(20) C. J. Collins, Z. K. Cheema, R. G. Werth, and B. M. Benjamin, *J. Amer. Chem. Soc.*, **86**, 4913 (1964).

(21) B. M. Benjamin and C. J. Collins, *ibid.*, **88**, 1556 (1966).

(22) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

3.02 (t), 4.6 (broad d). *Anal.* Calcd for $C_{20}H_{22}O_3S$: C, 70.15; H, 6.48. Found: C, 70.11; H, 6.64.

The compound with X = *p*-CH_3 had mp 86.5–87.5°, nmr δ 3.05 (t), 4.6 (d). *Anal.* Calcd for $C_{21}H_{24}O_3S$: C, 70.75; H, 6.79. Found: C, 70.39; H, 6.08.

The compound with X = *p*-Cl had mp 108.5–109°, nmr δ 2.94 (t), 4.43 (d). *Anal.* Calcd for $C_{20}H_{21}O_3SCl$: C, 63.72; H, 5.62. Found: C, 63.94; H, 5.50.

The compound with X = *m*-Cl had mp 87.5–88.5°, nmr δ 3.00 (t), 4.5 (broad s). *Anal.* Calcd for $C_{20}H_{21}O_3SCl$: C, 63.72; H, 5.62. Found: C, 63.44; H, 5.81.

endo-3-(X-Phenyl)-*endo*-2-norbornanol Tosylates.—The compound with X = H had mp 113–114° (reported 111–112°),[13] nmr δ 3.12 (2 d), 5.1 (2 d). *Anal.* Calcd for $C_{20}H_{22}O_3S$: C, 70.16; H, 6.48. Found: C, 70.29; H, 6.65.

The compound with X = *p*-CH_3 had mp 109–109.5°, nmr δ 3.03 (2 d), 5.0 (2 d). *Anal.* Calcd for $C_{21}H_{24}O_3S$: C, 70.77; H, 6.79. Found: C, 71.13; H, 7.00.

The compound with X = *p*-Cl had mp 123°, nmr δ 3.18 (2 d), 5.02 (2 d). *Anal.* Calcd for $C_{20}H_{21}O_3SCl$: C, 63.7; H, 5.62. Found: C, 63.6; H, 5.68.

The compound with X = *m*-Cl had mp 123–125°, nmr δ 3.04 (2 d), 5.06 (2 d). *Anal.* Calcd for $C_{20}H_{21}O_3SCl$: C, 63.7; H, 5.62; S, 8.50. Found: C, 63.6; H, 5.60; S, 8.40.

exo-3-(X-Phenyl)-*endo*-2-norbornanol Tosylate.—The compound with X = H had mp 99–100° (reported 96–97°),[13] nmr δ 2.52 [q(?)], 4.82 (t). *Anal.* Calcd for $C_{20}H_{22}O_3S$: C, 70.16; H, 6.48. Found: C, 69.6; H, 6.23.

exo-3-Phenyl-*exo*-2-norbornyl tosylate was prepared from the alcohol supplied by Professor D. C. Kleinfelter, University of Tennessee,[10,13] mp 101–102° (reported[13] 102–103°).

Kinetic Procedures.—Kinetic analyses were performed as described previously.[1] Olefin product yields were calculated from the measured extinction coefficients: 2-phenylnorbornene, ε 14,800 at λ_{max} 262.5 mμ (lit.[19] ε 10,715 at λ_{max} 262.5); 2-*p*-methylphenylnorbornene, ε 15,600 at λ_{max} 264.5 mμ (lit.[19] ε 12,023 at 264.0); 2-*p*-chlorophenylnorbornene, ε 18,800 at λ_{max} 267.5 mμ (lit.[19] ε 15,490 at 267.0); 2-*m*-chlorophenylnorbornene, ε 14,100 at λ_{max} 265.0 mμ.

Registry No.—A (Z = H), 23430-74-2; A (Z = *p*-CH_3), 23430-75-3; A (Z = *p*-Cl, 23430-76-4; A (Z = *m*-Cl), 23430-77-5; B (Z = H), 10472-58-9; B (Z = *p*-CH_3), 23430-79-7; B (Z = *p*-Cl, 23430-80-0; B (Z = *m*-Cl), 23430-81-1; C, 23430-82-2; D, 10472-63-6; 2-*p*-methylphenylnorbornene, 23430-54-8; 2-*m*-chlorophenylnorbornene, 23465-01-2; 2-*p*-chlorophenylnorbornene, 23430-55-9; *endo*-3-*p*-methylphenyl-*exo*-2-norbornanol, 23430-84-4; *endo*-3-*m*-chlorophenyl-*exo*-2-norbornanol, 23430-85-5; *endo*-3-*p*-chlorophenyl-*exo*-2-norbornanol, 23430-86-6; 3-(*p*-methylphenyl)-2-norbornanone, 23465-02-3; 3-(*p*-chlorophenyl)-2-norbornanone, 23430-56-0; 3-(*m*-chlorophenyl)-2-norbornanone, 23430-57-1; *endo*-(3-*p*-methylphenyl)-*endo*-2-norbornanol, 23430-87-7.

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Reexamination of Type II Elimination Reactions in the Photolysis of Aliphatic Carboxylic Acids and Amides

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Early and sparse accounts of the type II process in simple aliphatic carboxylic acids and amides have been scrutinized experimentally and conceptually. Little of a photochemical nature is known about these important classes of compounds, owing primarily to experimental problems. We have found the early work on these systems to be incomplete and possibly misleading, and thus present the results of our own study of products, quantum yields, and spectroscopy of the above compounds. The type II process does take place, from a high-lying probably n,π* state, in butyric and valeric acid. In the case of the amides, in contrast to a previous report, irradiation at 254 nm causes virtually no reaction of unsubstituted propionamide, butyramide, and valeramide. However, the N,N-dimethyl derivatives do decompose, *via* the type I process, relatively efficiently *via* an unspecified electronic state.

The type II photochemical elimination reaction has often been demonstrated to occur readily during the photolysis of such carbonyl compounds as aldehydes, ketones, keto acids, and certain esters; however, evidence for this reaction occurring with aliphatic carboxylic acids and amides is less conclusive. Indeed, very little about the latter processes is known, owing both to experimental difficulty and poor understanding of the relevant spectroscopic states.

Booth and Norrish[2] examined the gaseous products from the photolysis of the aliphatic amides propionamide (C_3), butyramide (C_4), valeramide (C_5), and hexanomide (C_6) dissolved in dioxane or hexane. They obtained some unsaturated hydrocarbon gas, which was established as ethylene (insoluble in concentrated sulfuric acid but soluble in fuming sulfuric acid) for the C_3 and C_4 amides, and inferred as propylene and butylene for the C_5 and C_6 amides, respectively. Despite the fact that more "ethylene" was obtained from propionamide than from butyramide and that none of the unsaturated gases was identified, the authors suggested that evidence for type II elimination existed. On the other hand Volman[3] found no photodecomposition of aliphatic amides in water at 25°. At 92° he found that the quantum yields for the formation of ammonia from acetamide, propionamide, and butyramide were 0.16, 0.023, and 0.029, respectively. He examined only the gaseous products of the photodegradation, but records no evidence for the formation of ethylene from any of the amides.

The gaseous products from the photolysis of butyric acid dissolved in isooctane or water were determined by Borrell and Norrish.[4] They found that ethylene was a

(1) Alfred P. Sloan Fellow, 1967–1970.

(2) G. H. Booth and R. G. W. Norrish, *J. Chem. Soc.*, 188 (1952).

(3) D. H. Volman, *J. Amer. Chem. Soc.*, **63**, 2000 (1941).

(4) P. Borrell and R. G. W. Norrish, *Proc. Roy. Soc., Ser. A*, **262**, 19 (1961).

major product from *n*-butyric acid but not from isobutyric acid, and that, whereas the production of other gaseous products was temperature dependent, suggesting a radical mechanism (type I reaction), the amount of ethylene formed was independent of temperature. By analogy with similar results obtained with ketones and esters they concluded that the ethylene resulted from the type II elimination reaction. Their proposed reactions were

$$\text{(type I)} \quad C_3H_7COOH \xrightarrow{h\nu} C_3H_7CO\cdot + \cdot OH$$

$$\text{(type II)} \quad C_3H_7COOH \xrightarrow{h\nu} C_2H_4 + CH_3COOH$$

In the above investigation no attempt was made to isolate and estimate the acetic acid, the other product in the type II reaction.

The purpose of the present investigation was to reexamine the photolysis of aliphatic acids and amides paying particular attention to the nongaseous products formed. As a secondary (and unfulfilled) hope, some understanding of the natures of the excited states was also sought.

Results and Discussion

Photolysis of Acids.—Irradiation at 253.7 nm of propionic, butyric, and valeric acids dissolved in dioxane or acetonitrile produced significant loss of starting material. One of the major products, apart from gaseous products, from butyric and valeric acids was acetic acid; no trace of acetic acid was detected in the product mixture from propionic acid.

Irradiation was carried out in a Rayonnet irradiator containing sixteen mercury resonance lamps. Accurate quantum yield determinations in this system presents a number of difficulties: the large output of the lamps rapidly exhausts the conventional actinometer solutions, no convenient filter systems are available, and cylindrical sample tubes are employed. Furthermore, irradiation at 253.7 nm is into the edges of the absorption bands of the acids where the extinction coefficients are quite small (<0.3), and, to use concentrations at which loss of starting material can be accurately determined, actinometer solutions with absorbances less than 1.0 are required. Some of these difficulties have been overcome (a) by using as the actinometer chloracetic acid which has an absorption curve at 253.7 nm similar in shape to the substances under investigation, (b) by ensuring that the initial absorbance at 253.7 nm (as determined on a nonscanning Carey 16 spectrophotometer) of all solutions, including the actinometer solutions, were identical (0.56 for 1-cm cells), (c) by restricting irradiation times to ensure no more than 10% loss of starting material, and (d) by bringing the temperature of all solutions to that of the irradiator (48°), which had been run for at least 1 hr to reach a stable temperature. For irradiations longer than 2 hr it was found necessary to replace the actinometer solutions every 2 hr. The value of 0.52 for the quantum yield for chloride ion formation at 48° was obtained from the work of Smith, Leighton, and Leighton.[5]

(5) R. N. Smith, P. A. Leighton, and W. G. Leighton, *J. Amer. Chem. Soc.*, **61**, 2299 (1939).

Utilizing this method of actinometry, the quantum yields for the disappearance of acid (Φ loss) and formation of acetic acid (Φ acid) in dioxane as solvent were determined; the values are given in Table I. The

TABLE I
PHOTOLYSIS OF ACIDS IN DIOXANE IRRADIATED AT 48° WITH 253.7 nm

Acid	Concentration,[a] *M*	Φ loss[b]	Φ acid[c]
Propionic	2.8	0.19	0.00
Butyric	1.75	0.16	0.05
Valeric	1.75	0.16	0.08

[a] Concentration required to give an absorbance of 0.56 in 1-cm cell at 253.7 nm. [b] Quantum yield for acid loss. [c] Quantum yield for acetic acid formation.

values for acetic acid formation include a small correction factor for the degradation of the acetic acid formed; this was determined by irradiating a solution of propionic acid (from which it had previously been shown no acetic acid formed) containing 5% acetic acid. Very little acetic acid photolysis occurs since it has a much lower extinction coefficient at 253.7 nm compared with the other acids and having such a low concentration, it absorbs very little of the energy available. Similar results to those shown in Table I were obtained with acetonitrile as solvent, but the quantum yields were less accurate owing to discoloration of the solvent after several hours irradiation.

The isolation of acetic acid from butyric and valeric acids is evidence that type II elimination does take place during photolysis of these acids. The results of Borrell and Norrish,[4] based only on evolved gases, have now been much more firmly substantiated. The higher value of Φ acid for valeric acid compared with butyric acid is to be expected since it has been shown[6] that secondary hydrogens are more readily extracted from the γ carbon than are primary hydrogens.

Excitation of Acids by Energy Transfer.—Since the absorbance at 253.7 nm of aliphatic acids in solution is so low (<0.3), the possibility of sensitizing the photolysis by intra- and intermolecular energy transfer from benzene, which absorbs relatively strongly at this wavelength, was investigated. 4-Phenylbutyric and 5-phenylvaleric acids dissolved in cyclohexane were irradiated and examined for the formation of acetic acid styrene, acetic acid, and allyl benzene, respectively. Loss of starting material was also monitored. These materials showed small loss of starting material, but apparently intramolecular energy transfer failed (as also indicated by emission measurements, *vide infra*) since no acetic acid or other expected degradation products of the starting materials were detected. Cursory spectral observation indicated that photolysis is restricted to the benzene ring. Intermolecular energy transfer was also ineffective. Irradiation of butyric and valeric acids in benzene solution yielded no loss of starting material, even after 24 hr of continuous irradiation. However, the benzene solutions became quite yellow, as did the pure solvent control sample, indicating considerable photodegradation of benzene with formation of polymeric material. From these results it is apparent, therefore, that photolysis of carboxylic acids cannot be sensitized by energy transfer from the benzene ring.

(6) P. J. Wagner and G. S. Hammond, *ibid.*, **87**, 4009 (1965).

Apparently the triplet energy of the carboxyl group is higher than that of benzene.

Phosphorescence Spectra.—An examination of the phosphorescence spectra, at 77°K, of a series of phenyl derivatives of acids dissolved in EPA gave spectra which were simply those of perturbed benzene phosphorescence, the perturbation decreasing as the carbon chain length increased. Spectra very similar to that obtained from propyl benzene were recorded for 4-phenylbutyric and 5-phenylvaleric acids.

Other Products.—It was noted that irrespective of the reagent being photolyzed in spectroquality cyclohexane, the same major product was isolated by vapor phase chromatography after photolysis for 15–24 hr periods; this product was ultimately identified as bicyclohexyl. Subsequently, it was found that irradiation of the pure Spectrograde solvent also produced bicyclohexyl but in small yields compared with that obtained with the more highly absorbing solutions. This product is undoubtedly formed by the extraction of hydrogen from the cyclohexane.

In most of these investigations using prolonged irradiation with a bank of 253.7-nm lamps, the stability of the solvents has presented difficulties. Degradation products from the solvents have altered the absorbance of the solutions and have complicated the vapor phase chromatographic analyses of the photolysis products. Of the solvents used, benzene degrades quite rapidly, acetonitrile and cyclohexane to a limited extent, whereas dioxane appeared relatively stable.

Photolysis of Amides.—Even after prolonged irradiation (in excess of 24 hr) at 253.7 mn, no loss of amide nor the presence of any photochemical degradation product could be detected in solutions of acetamide, propionamide, butyramide, and valeramide dissolved in dioxane or acetonitrile. This result is in conflict with the report of Norrish[2] in the days prior gas chromatography. It is apparent, therefore, that these amides are quite resistant to photolysis at 48° in these solvents, in accordance with Volman's work[3] which showed that amides were resistant to photolysis in water at 25° but some photodecomposition occurred at temperatures in excess of 50°.

When solutions of the N,N-dimethyl derivatives of acetamide, propionamide, and butyramide were photolyzed in cyclohexane (0.04–0.05 *M*) and dioxane (0.16–0.20 *M*) significant loss of amide was detected. The quantum yields recorded are given in Table II.

TABLE II

PHOTOLYSIS OF N,N-DIMETHYLAMIDES IRRADIATED WITH 253.7 nm AT 48°

	Φ loss, reagent	
	Cyclohexane	Dioxane
N,N-Dimethylacetamide	0.12	0.10
N,N-Dimethylpropionamide	0.16	0.12
N,N-Dimethylbutyramide	0.15	0.12

Examination by gas chromatography of the solutions after photolysis indicated a complex mixture of products, all in very low concentrations. A careful examination of the products from the photolysis of N,N-dimethylbutyramide revealed no trace of N,N-dimethylacetamide, certainly one of the products expected if the type II elimination had occurred. To eliminate the possibility that some N,N-dimethylacetamide had been produced, but was itself immediately photolyzed, equal amounts of N,N-dimethylacetamide (equivalent to 5% conversion of the butyramide by the type II process) were added to solutions, of equal absorbance, of the N,N-dimethyl derivatives of propionamide and butyramide. There was a just perceptible, but equal, loss of the acetamide derivative in each case, indicating that no N,N-dimethylacetamide had been produced from the butyramide by the type II elimination reaction.

The absence of evidence for type II elimination indicates that the photolysis of N,N-dimethylamides proceeds by a type I reaction with breakdown of the C–N bond as follows

$$RCON(CH_3)_2 \xrightarrow{h\nu} \begin{matrix} R - \dot{C}O + \cdot N(CH_3)_2 \\ R\cdot + CO \end{matrix}$$

with the alkyl and dimethylamine radicals interacting in a variety of ways. The complexity of the photolysis product mixture indicated that some of the likely photolysis products such as tetramethyl hydrazine and dimethyl propylamine (which we detected in the photolysis of N,N-dimethylbutyramide) underwent subsequent photolysis. Reasons for the greater stability to photochemical degradation of the unsubstituted amides relative to the N,N-dimethyl derivatives are not apparent at present.

It is surprising to find that whereas aliphatic acids undergo type II photochemical elimination, the corresponding amides or N,N-disubstituted amides do not. One possible explanation may be that amide absorption is due to a "charge-transfer" transition, as proposed by Neilsen and Schellman,[7] whereas acids have no such transition (leading to a corresponding excited state) but rather are excited $n \rightarrow \pi^*$. However, much more information than is presently available about the excited states of the carboxyl and amide groups will be required before a satisfactory explanation for this apparent anomaly can be reached.

Experimental Section

Chemicals.—All materials were commercially available. The acids, N,N-dimethylamides and chloracetic acid were purified by distillation, the amides by recrystallization from acetone–hexane and the phenyl derivatives of the acids from hexane. The solvents, dioxane, acetonitrile, benzene, and cyclohexane, were Matheson Coleman and Bell Spectrograde, used without further purification.

Spectra.—Absorption spectra were recorded on a Perkin-Elmer 202 spectrophotometer. Absorbances at 253.7 nm were measured on a Carey 16 spectrophotometer. Emission spectra were taken with an Aminco–Bowman spectrofluorometer.

Irradiation.—Samples (5 ml) were degassed and sealed in 15-mm quartz tubes and supported on a revolving tube holder inside a Rayonnet irradiator containing 16 253.7-nm Westinghouse Sterilamp G 8T5 tubes.

Actinometry.—After the lamps had been running for 1 hr to allow the irradiator to reach temperature equilibrium, the actinometer solution, 5 ml of 0.5 *M* chloracetic acid (absorbance 0.56 at 253.7 nm), in a 15-mm quartz tube was inserted, together with the preheated degassed samples, into the rotating tube holder. For irradiations longer than 2 hr the actinometer tubes

(7) E. B. Neilsen and J. A. Schellman, *J. Phys. Chem.*, **71**, 3914 (1967).

were replaced each 2 hr. The chloride ion formed was estimated by volumetric titration with mercuric nitrate.[8]

Analysis of Products.—All nongaseous products were detected by gas chromatography, using a 1/4-in. column packed with 5% FFAP on Chromosorb W, and compared with authentic samples.

Registry No.—Propionic acid, 79-09-4; butyric acid, 107-92-6; valeric acid, 109-52-4; N,N-dimethylacetamide, 127-19-5; N,N-dimethylpropionamide, 758-96-3; N,N-dimethyllbutyramide, 760-79-2.

(8) "Standard Methods for the Examination of Water and Waterwaste," 12th ed, American Public Health Association, New York, N. Y., 1965, p 87.

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Steric Effects in Intramolecular Rearrangements Involving a [3.2.1]-Bicyclic Mechanism[1]

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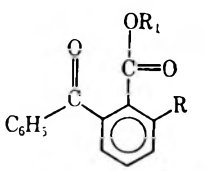
Pyrolyses of 1-ethoxyvinyl 2-benzoylbenzoate (**5**), 1-ethoxyvinyl 6-methyl-2-benzoylbenzoate (**6**), 1-ethoxyvinyl 3-methyl-2-benzoylbenzoate (**7**), and 1-ethoxyvinyl 3,6-dimethyl-2-benzoylbenzoate (**8**) have been studied. Qualitative studies show that the methyl group in the 6 position facilitates the rearrangement to lactone ester whereas a methyl group in the 3 position hinders the rearrangement. An explanation for the facts is presented.

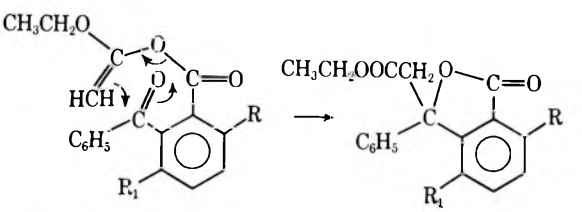
The idea that bicyclic mechanisms might be involved in organic reactions arose from the facts that the rate of alkaline hydrolysis of methyl 6-methyl-2-benzoylbenzoate (**1**) is greater than that of methyl 2-benzoylbenzoate[2] (**2**) and the rate of acid-catalyzed esterification of 6-methyl-2-benzoylbenzoic acid (**3**) is greater than that of 2-benzoylbenzoic acid[3] (**4**). These facts were explained by assuming that attack of the reagent in question took place mainly at the ketonic group rather than at the carbonyl group of the carboxyl function.



1, R = CH_3; R_1 = CH_3
2, R = H; R_1 = CH_3
3, R = CH_3; R_1 = H
4, R = H; R_1 = H

By synthesizing compounds which had functions at R_1 which could lead to intramolecular cyclization, reactions were found to occur on pyrolysis in which groups ended up preferentially on the ketonic carbonyl carbon rather than the carboxylic carbon. The mechanisms by which these reactions occur have been termed bicyclic mechanisms.[4]

In previous work, no study of steric effects on the rate of reactions proceeding by bicyclic mechanisms was made. In this paper the relative rate of thermal rearrangement of ethoxyvinyl 2-benzoylbenzoate (**5**), ethoxyvinyl 6-methyl-2-benzoylbenzoate (**6**), and ethoxyvinyl 3,6-dimethyl-2-benzoylbenzoate (**8**) to the corresponding lactone esters 5_{LE}, 6_{LE}, and 8_{LE} have



5, R = R_1 = H
6, R = CH_3; R_1 = H
7, R = H; R_1 = CH_3
8, R = R_1 = CH_3

5_{LE}
6_{LE}
7_{LE}
8_{LE}

been determined qualitatively. As the rate of rearrangement of **6** was greater than that for **5**, **7**, and **8**, the steric assistance noted in alkaline hydrolysis[2] and acidic esterification[3] is also of importance in the intramolecular [3.2.1]-bicyclic rearrangement. However, the presence of a methyl group in the 3 position in compounds **7** and **8** retards the bicyclic path strongly. In the case of **7** rearrangement to 7_{LE} did not occur. Instead, at the temperature of 200–220° needed for pyrolysis, only the normal-pseudo anhydride of 3-methyl-2-benzoylbenzoic acid was formed. Since pyrolysis of **8** gives mainly 8_{LE}, another example of the favorable effect of a methyl group in the 6 position is provided as it overcomes the unfavorable effect of the methyl group at the 3 position.

The favorable effect of the 6-methyl group in the rearrangements of **6** and **8** relative to **5** and **7**, respectively, is probably due to two factors: (a) the steric effect of the 6-methyl group which keeps the carboxyl function from coplanarity with the ring (raising the energy of the ground state for the rearrangement) and (b) the relief of strain in the product (lowering the energy of the transition state). The adverse effect of the 3-methyl group probably acts mainly by increasing

(1) This research was supported in part by Grant 5552 of The National Science Foundation and by Grant DA-ARO-D-31-124-G846 from the U. S. Army Research Office, Durham, N. C.

(2) M. S. Newman and S. Hishida, *J. Amer. Chem. Soc.*, **84**, 3582 (1962).

(3) M. S. Newman and C. Courduvelis, *J. Org. Chem.*, **30**, 1795 (1965).

(4) A bicyclic mechanism is defined as an intramolecular cyclic mechanism in which the atoms involved in change of bonding are not in a continuous chain. In cyclic mechanisms the atoms involved form a continuous chain. For examples of [3.2.1]-, [3.3.1]-, and [4.2.2]-bicyclic mechanisms, see the following articles and references therein: (a) M. S. Newman and C. Courduvelis *J. Amer. Chem. Soc.*, **88**, 781 (1966); (b) M. S. Newman, S. Mladenovic, and L. K. Lala, *ibid.*, **90**, 747 (1968).

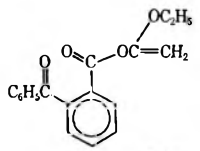
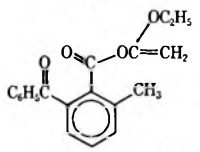
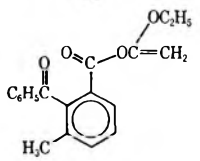
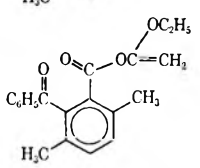
the energy of the transition state due to conventional steric hindrance to addition to a carbonyl group.

The requisite 2-benzoylbenzoic acids were prepared by known methods (see Experimental Section). The mixture of 6-methyl-2-benzoylbenzoic acid (6_A) and 3-methyl-2-benzoylbenzoic acid (7_A) obtained by the Friedel–Crafts condensation of 3-methylphthalic anhydride with benzene[5] was separated in part into the two pure acids by fractional recrystallization. By heating a mixture of 6_A and 7_A in 100% sulfuric acid solution at 70° the mixture was converted in high yield to almost pure 6_A.[6]

The ethoxyvinyl esters, **5**–**8**, prepared as described,[4a,7] were heated neat in carefully cleaned flasks to give the results listed in Table I. Previously, thermal rearrangement of the mixed anhydride of methyl carbonic and *o*-benzoylbenzoic acids was shown to occur unimolecularly.[8] We assume that the analogous thermal rearrangement of the ethoxyvinyl esters is also unimolecular.

TABLE I

PYROLYSES OF ETHOXYVINYL ESTERS

Compd		Temp, °C[a]	Lactone–ester[b]	Anhydride[c]
5		180	>90	None
6		150	80	10
7		200[d]		>90
8		200	85	8[e]

[a] Temperature needed for 1 hr of pyrolysis to cause a minimum of 95% disappearance of starting vinyl ester. [b] Per cent isolated as lactone–ester. [c] Isolated yields of n,ψ-anhydrides.[4a] [d] Pyrolysis of **7** for 2 hr yielded only the n,ψ-anhydride. [e] The structure of this anhydride is uncertain (see Experimental Section).

The rearrangements of **5** and **7** to 5_{LE} and 7_{LE} was markedly catalyzed by boron fluoride etherate. Presumably these acid-catalyzed rearrangements also occur by a [3.3.1]-bicyclic mechanism. Additional examples of boron fluoride catalyzed bicyclic rearrangements are to be presented in the near future.

Interestingly the α hydrogens of the acetic ester grouping in 6_{LE} (and of the corresponding acetic acid grouping) appear as a singlet on the 60-Mc instrument whereas the corresponding methylene hydrogens in 7_{LE} and 8_{LE} appear as an AB quartet.

Experimental Section[9]

3-Carbethoxymethyl-3-phenylphthalide (5_{LE}).—Pure 1-ethoxyvinyl 2-benzoylbenzoate (**5**), mp 74–75°, prepared as described[4a] and recrystallized from benzene–hexane, was obtained in 92% yield. On pyrolysis at 200° for 30 min 5_{LE} was produced exclusively. Crystallization from benzene–hexane yielded colorless crystals, mp 95–96°, in over 90% yield.

On allowing a solution of 2.0 g of **5** in 50 ml of methylene chloride containing a few drops of boron trifluoride etherate to stand for 12 hr at room temperature pure 5_{LE} was produced in 85% yield.[10]

1-Ethoxyvinyl 6-Methyl-2-benzoylbenzoate (**6**).—The preparations of the ethoxyvinyl esters were carried out as described.[4a] Using 6-methyl-2-benzoylbenzoic acid[5] yields of 61–81% pure **6** were obtained: mp 75.0–75.5°; nmr 8.75 (t, 3 H, J = 7.5 Hz, OCH_2CH_3), 7.47 (s, 3 H, $ArCH_3$), 6.55–6.00 (m, 4 H, OCH_2CH_3, $OC{=}CH_2$ the dd of $OC{=}CH_2$ is not distinguishable from the quartet of OCH_2CH_3), 2.85–2.12 (m, 8 H, ArH).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.5; H, 5.9. Found: C, 73.2; H, 5.7.

3-Carbethoxymethyl-7-methyl-3-phenylphthalide (6_{LE}).—On pyrolysis of 1.0 g of **6** at 160° for 1 hr and trituration of the cooled mixture with ether, there was obtained 0.15 g of a solid, mp 184–186°, and an oily remainder. Recrystallization from benzene–ligroin yielded the pure n,ψ-anhydride: mp 186–187°; nmr 7.63 (s, 3 H, $ArCH_3$), 7.46 (s, 3 H, $ArCH_3$), 2.88–2.28 (m, 16 H, ArH). The different methyl signals rule out n,n- and ψ,ψ-anhydrides.

Anal. Calcd for $C_{30}H_{22}O_5$: C, 77.7; H, 4.8. Found: C, 77.7, 77.9; H, 4.8, 5.1.

Bulb-to-bulb distillation of the oil [air bath at 170–175° (0.002 mm)] yielded 0.8 g (80%) of an oil. Redistillation with little loss afforded oily 6_{LE}: nmr 9.01 (t, 3 H, J = 7.5 Hz, OCH_2CH_3), 7.30 (s, 3 H, $ArCH_3$), 6.60 (s, H, CH_2CO), 6.10 (q, 2 H, J = 7.5 Hz, OCH_2CH_3), 2.90–2.33 (m, 8 H, ArH).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.5; H, 5.9. Found: C, 73.5; H, 6.2.

Alkaline hydrolysis yielded 3-carboxymethyl-7-methyl-3-phenylphthalide: mp 169–170°; nmr (acetone-d_6), 7.31 (s, 3 H, $ArCH_3$), 6.40 (s, 2 H, CH_2CO), 2.68–2.32 (m, 8 H, ArH), 2.30 (s, 1 H disappears on adding D_2O, COOH), in high yield.

Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.3; H, 5.0. Found: C, 72.1; H, 4.8.

1-Ethoxyvinyl 3-Methyl-2-benzoylbenzoate (**7**).—By treatment of 4.8 g of 3-methyl-2-benzoylbenzoic acid[5] with ethoxyacetylene[4a] there was obtained 5.9 g (95%) of colorless **7**, mp 98–101°. Recrystallization from benzene–hexane with little loss yielded **7**: mp 101–102°; nmr 8.83 (t, 3 H, J = 7.5 Hz, OCH_2CH_3), 7.89 (s, 3 H, $ArCH_3$), 6.57–6.13 (m, 4 H, OCH_2CH_3, $OC{=}CH_2$, the dd of $OC{=}CH_2$ is not distinguishable from the quartet of OCH_2CH_3), 3.00–2.18 (m, 8 H, ArH).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.5; H, 5.8. Found: C, 73.7; H, 5.6.

After treatment of 1.8 g of **7** in methylene chloride with boron trifluoride ethereate as described above[9] for **5**, the methylene chloride was removed on a rotary evaporator. By crystallization of the residue from benzene–hexane there was isolated 0.6 g (45%) of the n,ψ-anhydride, mp 165–168°. A recrystallized sample melted at 168–169°; nmr 8.08 (s, 3 H, $ArCH_3$), 7.92 (s, 3 H, $ArCH_3$), 2.78–2.28 (m, 16 H, ArH). On alkaline hydrolysis 3-methyl-2-benzoylbenzoic acid[5] was obtained.

Anal. Calcd for $C_{30}H_{22}O_5$: C, 77.7; H, 4.8. Found: C, 77.5; H, 4.8.

On bulb-to-bulb distillation [bath temperature 165–170° (0.001 mm)] there was obtained 0.43 g (24%) of **7** as a pale yellow oil: nmr 9.10 (t, 3 H, J = 7.0 Hz, OCH_2CH_3), 7.83 (s, 3 H,

(5) M. S. Newman and C. D. McCleary, *J. Amer. Chem. Soc.*, **63**, 1542 (1941).

(6) For an explanation, see M. S. Newman and K. G. Ihrman, *ibid.*, **80**, 3652 (1958).

(7) H. H. Wasserman and P. S. Wharton, *ibid.*, **82**, 661 (1960).

(8) M. S. Newman and L. K. Lala, *J. Org. Chem.*, **32**, 3225 (1967).

(9) All melting points and boiling points are uncorrected. Analyses were done by Galbraith Microanalytical Laboratories, Knoxville, Tenn. All flasks used for pyrolysis experiments were steamed for 30 min and dried before use. The ethoxyacetylene used (Farchan Laboratories, Willoughby, Ohio) was redistilled and stored in ampoules in the cold chamber of a refrigerator until used. When pure, ethoxyacetylene can be stored thus for long periods. Nmr spectra were taken in $CDCl_3$ and are expressed in τ relative to $(CH_3)_4Si$, 10.0.

(10) D. Cohen and G. E. Pattenden, *J. Chem. Soc. C*, 2314 (1967).

$ArCH_3$), 6.40–5.92 (m, 4 H, CH_2CO, OCH_3CH_3, the dd of CH_2CO is not distinguishable from the quartet of OCH_2CH_3), 2.78–2.10 (m, 8 H, ArH).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.5; H, 5.8. Found: C, 73.9; H, 5.9.

On pyrolysis of 0.80 g of 7 at 200° for 2 hr there was obtained 0.6 g (97%) of n,ψ-anhydride, mp and mmp (with above anhydride) 168–169°.

1-Ethoxyvinyl 3,6-Dimethyl-2-benzoylbenzoate (8).—Treatment of 3,6-dimethyl-2-benzoylbenzoic acid[11] as described[4a] yielded 8, mp 73–75° in almost quantitative yield. Recrystallization from ether–petroleum ether (bp 30–60°) gave with little loss colorless 8: mp 74.5–75.5°; nmr 8.77 (t, 3 H, J = 7.5 Hz, OCH_2CH_3), 7.89, 7.49 (each s, 3 H, $ArCH_3$), 6.53 (dd, 2 H, J = 3.5 Hz, $=CH_2$), 6.30 (q, 2 H, J = 7.5 Hz, OCH_2CH_3), 2.88–2.10 (m, 7 H, ArH).

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.1; H, 6.2. Found: C, 73.9; H, 6.2.

3-Carboethoxymethyl-4,7-dimethyl-3-phenylphthalide (8_{LE}).—Pyrolysis of 4.68 g of 8 at 220–230° for 1 hr yielded a mixture which on trituration afforded 0.55 (8%) of solid, mp 255–260°. After two recrystallizations from benzene–petroleum ether a solid, mp 278–280°, was obtained with little loss. Because of limited solubility no nmr was run. We are uncertain of the structure of this anhydride.

Anal. Calcd for $C_{32}H_{26}O_5$: C, 78.3; H, 5.3. Found: C, 78.6; H, 5.7.

Bulb-to-bulb distillation of the remainder of the pyrolysis products (0.05 mm) yielded a liquid which was redistilled to yield 4.1 g (85%) of 8_{LE} as a pale yellow oil which distilled (two-bulb system) with the heating bath at 185–190° (0.0014 mm); nmr 9.05 (t, 3 H, J = 7.0 Hz, OCH_2CH_3), 7.88, 7.30 (each s, 3 H, $ArCH_3$), 6.38 (dd, 2 H, J = 14.8 Hz, CH_2CO), 6.11 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 2.70 (each s, 7 H, ArH).

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.1; H, 6.2. Found: C, 73.9; H, 6.3.

3-Carboxymethyl-4,7-dimethyl-3-phenylphthalide.—On hydrolysis with barium hydroxide, 2.0 g of 8_{LE} yielded 1.4 g (89%) of colorless needles (from chloroform–benzene) of acid: mp 155.0–155.5°; nmr (acetone-d_6), 7.84, 7.31 (each s, 3 H each, $ArCH_3$), 6.24 (dd, J = 15.0 Hz, CH_2CO), 2.63 (s, 1 H, disappears on addition of D_2O, COOH), 2.58 (s, 7 H, ArH).

Anal. Calcd for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 73.0; H, 5.5.

Pyrolysis Experiments, Table I.—The esters 5–8 were heated in flasks which had been steamed out for 30 min and dried. Disappearance of nmr bands in the τ 6.33–6.48 region (characteristic of the vinyl hydrogens) was taken as a measure of completion of reaction.

Registry No.—**5**, 6158-56-1; 5_{LE}, 6158-57-2; **6**, 24766-40-3; **6** anhydride, 24766-41-4; 6_{LE}, 24766-42-5; **7**, 24766-43-6; **7** anhydride, 24766-44-7; **8**, 24766-45-8; 8_{LE}, 24766-46-9; 3-carboxymethyl-7-methyl-3-phenylphthalide, 24766-47-0; 3-carboxymethyl-4,7-dimethyl-3-phenylphthalide, 24766-48-1.

(11) M. S. Newman and B. T. Lord *J. Amer. Chem. Soc.* **66**, 733 (1944).

The Acid-Catalyzed Nitramine Rearrangement. VII. Intramolecularity[1-3]

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Concurrent rearrangement of N-nitro-N-methylaniline and *p*-fluoro-N-nitro(^{15}N)-N-methylaniline yielded *p*-nitro-N-methylaniline containing a considerable excess of ^{15}N. This indication of intermolecularity in the nitramine rearrangement was strengthened by the exclusion of other possible pathways for the formation of *p*-nitro(^{15}N)-N-methylaniline. It was found that the yields of nitroanilines were reduced and the nitro-group exchange was eliminated in the presence of reducing agents, suggesting that they intercept the species involved in the intermolecular process. These results are readily interpreted in terms of a previously proposed mechanism.

Most mechanisms for the nitramine rearrangement are based upon the need to account for the intramolecularity of the reaction. A varied series of studies support the assumption of intramolecularity. Rearrangement of N-nitroaniline in 85% sulfuric acid at 10° yielded only *o*- and *p*-nitroanilines while nitration of aniline under similar conditions gave chiefly the *meta* and *para* isomers.[4,5] If the nitramine dissociated into aniline and nitronium ion during the rearrangement, then the product should have been identical to that from direct nitration.

A number of investigators have shown that a nitro group is not transferred from rearranging nitramine to an easily nitratable substance added to the reaction medium. Thus, the acid-catalyzed rearrangement of 2,4,6-tribromo-N-nitroaniline in the presence of either acetanilide or 2,4-dichloroaniline failed to produce nitroacetanilide or 2,4-dichloro-6-nitroaniline.[6] Similarly, it was found that when N,4-dinitro-N-methylaniline was converted to 2,4-dinitro-N-methylaniline in the presence of xylene or phenol, no nitroxylenes or nitrophenols were formed and no *p*-nitro-N-methylaniline (from loss of a nitro group) could be detected. Thus, no substance that could nitrate acetanilide, 2,4-dichloroaniline, *p*-xylene, or phenol existed during these rearrangements. However, the behavior of N,2,4-trinitro-N-methylaniline[5] is somewhat paradoxical. In 80% sulfuric acid, this compound yielded the expected product, 2,4,6-trinitro-N-methylaniline, but in other acid media, such as dilute hydrochloric acid and acetic–sulfuric acid mixtures, the denitration product, 2,4-dinitro-N-methylaniline, was obtained. Furthermore, when the rearrangement was conducted in sulfuric acid in the presence of *p*-xylene, 2-nitro-1,4-xylene and 2,4-dinitro-N-methylaniline were isolated

(1) Previous papers in this series: (a) W. N. White, D. Lazdins, and H. S. White, *J. Amer. Chem. Soc.*, **86**, 1517 (1964); (b) W. N. White, C. Hathaway, and D. Huston, *J. Org. Chem.*, **35**, 737 (1970); (c) W. N. White and J. R. Klink, *ibid.*, **35**, 965 (1970); (d) W. N. White, J. T. Golden, and D. Lazdins, *ibid.*, **35**, 2048 (1970); (e) W. N. White and H. S. White, *ibid.*, **35**, 1803 (1970).

(2) Part of this work has been reported in a preliminary form: W. N. White, J. R. Klink, D. Lazdins, C. Hathaway, J. T. Golden, and H. S. White, *J. Amer. Chem. Soc.*, **83**, 2024 (1961).

(3) This work was supported by Grants G-7345 and GP-1970 from the National Science Foundation.

(4) A. F. Holleman, J. C. Hartogs, and T. van der Linden, *Ber.*, **44**, 704 (1911).

(5) E. D. Hughes and G. T. Jones, *J. Chem. Soc.*, 2678 (1950).

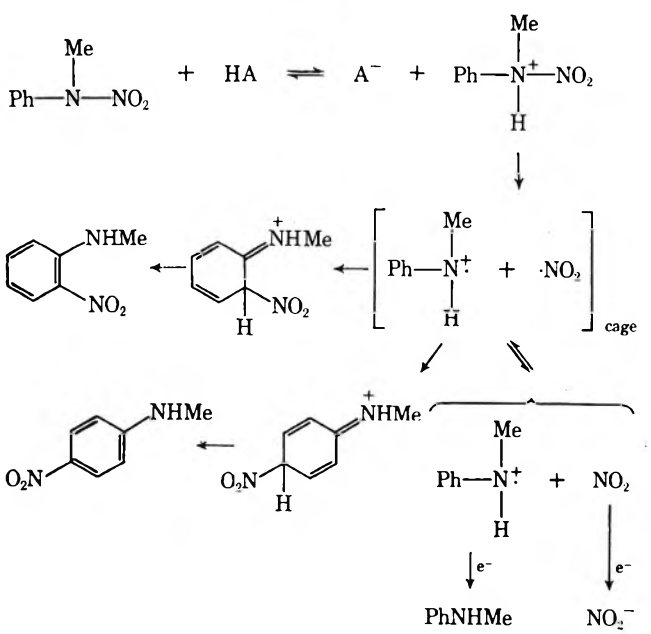
(6) K. J. P. Orton, *Chem. News*, **106**, 236 (1912).

along with the usual rearrangement product. This evidence might suggest that rearrangement was occurring by dissociation of the substrate into nitronium ion and 2,4-dinitro-N-methylaniline followed by reaction of these species to form the isomerization product. Other easily nitratable substances could also then react with the nitronium ion. Weak acids would be of insufficient strength to affect the renitration. However, this interpretation is apparently incorrect. It was found impossible to nitrate 2,4-dinitro-N-methylaniline in 80% sulfuric acid, while *p*-xylene was converted to 2,3-dinitro-1,4-xylene. In addition, although nitration of phenol in 80% sulfuric acid gave nitrophenol, the latter product was not obtained when the trinitro compound was rearranged in the same medium in the presence of phenol even though 2,4-dinitro-N-methylaniline, the denitration product, was formed from the nitramine.

Additional evidence supporting an intramolecular course for the rearrangement was obtained by rearranging N-nitroaniline[7] and N-nitro-N-methyl-1-naphthylamine[8] in the presence of ^{15}N-labeled nitric acid and ^{15}N-labeled potasssium nitrite. In no case was an appreciable excess of ^{15}N detected in the nitrated products indicating that the nitramine nitro group did not become equilibrated with the pool of nitric or nitrous acid in the medium.

In spite of this overwhelming evidence for the intramolecularity of the nitramine rearrangement, there are some bothersome unexplained discrepancies such as the above-described reactions of N,2,4-trinitro-N-methylaniline. Recently reported studies of the effect of reducing agents on the rearrangement of N-nitro-N-methylaniline[1e] can be most reasonably interpreted on the basis of the following mechanism (Chart I) which involves an intermolecular pathway as a side reaction. All of the above quoted evidence for intramolecularity

CHART I



can be interpreted on the basis of this mechanism. Only *ortho*- and *para*-substituted products would be formed since significant odd-electron density in the anilinium radical occurs only at these positions. Nitration of easily nitratable foreign substances would not be expected unless the caged radicals dissociate and a reducing agent is present to reduce nitrogen dioxide to nitrous acid. The latter may then cause nitration through nitrosation or it may disproportionate to nitric acid. The perplexing results with N-2,4-trinitro-N-methylaniline become understandable in terms of this mechanism. The rearrangement of this compound may be largely intermolecular. In the absence of a reducing agent the dissociated radicals recombine to form a rearrangement product. However, in the presence of a reductant the normal reaction is diverted: denitration product and nitrous acid are formed from the nitramine. Phenol, if present, will be nitrosated and the resulting compound will be polymerized by the strong acid. Nitration of xylene may also occur through nitrosation. Product incorporation of ^{15}N from ^{15}N-labeled nitrous or nitric acid in the medium would not be expected since the oxidation state of the nitrogen in the rearrangement intermediate is different.

These considerations make it seem likely that the nitramine rearrangement may have an intermolecular component in those cases where dissociation of the caged radicals occurs at a rate similar to or faster than rebonding of the radicals in the cage to form the intermediates leading to nitrated products.

If the aromatic nitramine rearrangement is, in part, intermolecular, then crossover of a nitro group from one molecule to another should occur. An attempt to detect this exchange was made by concurrently rearranging N-nitro-N-methylaniline and *p*-fluoro-N-nitro(^{15}N)-N-methylaniline.

Results and Discussion

Rearrangement of a mixture of *p*-fluoro-N-nitro(^{15}N)-N-methylaniline and N-nitro-N-methylaniline did, in fact, result in an excess of ^{15}N in a product from the unlabeled nitramine (Table I). This indicates that the nitro groups from the two nitramines became mixed in solution and returned indiscriminately to the two different aniline moieties. Thus, the nitramine rearrangement is at least partially intermolecular.

TABLE I

^{15}N CONTENTS OF REARRANGEMENT[a] PRODUCTS OF MIXED NITRAMINES

10^4 *M* PhNMeNO2	10^4 *M* *p*-FC6H4-NMeN^{15}O2[b]	10^4 *M* *p*-HOC6H4-OH	% ^{15}N in *p*-O2NC6H4NHMe Found	Calcd
5.64	4.41	0.00	2.9	3.1
2.48	4.41	0.00	4.5	4.2
5.15	4.42	25.50	0.4[c]	0.4[c]

[a] $HClO_4$ = 0.511 *M*, $NaClO_4$ = 0.500 *M*, HSO_3NH_2 = 0.05 *M*, 40.0°. [b] 13.6% ^{15}N. [c] Natural abundance of ^{15}N is 0.4%.

The per cent of ^{15}N expected in the *p*-nitro-N-methylaniline may be calculated from the following pieces of information: (1) the molarity of each nitramine in the mixture, (2) the per cent of ^{15}N in each of these compounds, (3) the rearrangement rates of each

(7) S. Brownstein, C. A. Bunton, and E. D. Hughes, *J. Chem. Soc.*, 4354 (1958); D. V. Banthorpe, E. D. Hughes, and D. L. H. Williams, *ibid.*, 5349 (1964).

(8) D. V. Banthorpe, J. A. Thomas, and D. L. H. Williams, *ibid.*, 6135 (1965).

nitramine, (4) the degree of intermolecularity in the reaction of each nitramine, and (5) the percentage of each nitrated product formed. The first of these pieces of data was obtained during the preparation of the solution. The second was available from the direct determination of the ^{15}N contents of the nitramines. The rate of reaction of N-nitro-N-methylaniline under the conditions of the concurrent rearrangement was 1.5×10^{-3} sec^{-1} or almost identical with the rearrangement rate of *p*-fluoro-N-nitro-N-methylaniline (1.6×10^{-3} sec^{-1}) under similar circumstances (Table II). To simplify the calculations these rates were assumed to be identical.

TABLE II

NITRAMINE REARRANGEMENT[a] PRODUCTS AND RATES

Compound	10^4 *M* *p*-HOC_6H_4-OH	10^3 k_1 (sec^{-1})	Products % 2	Products % 4
$PhNMeNO_2$	0.00	1.5	49	31
	2.20	1.5	42	19
p-$FC_6H_4NMeNO_2$	0.00	1.6	78	
	2.20	1.6	47	

[a] $HClO_4$ = 0.511 *M*, $NaClO_4$ = 0.500 *M*, HSO_3NH_2 = 0.05 *M*, 40°.

It was shown in previous work[1e] that a fraction of the nitramine rearrangement could be diverted by reducing agents and that this portion of the reaction corresponds to an intermolecular component of the process: dissociated free radicals capable of reduction are formed. Thus, it should be possible to determine the extent of intermolecularity by finding the amount of rearrangement which can be diverted in the presence of a reducing agent. Rearrangement of N-nitro-N-methylaniline and *p*-fluoro-N-nitro-N-methylaniline were carried out in the presence and absence of hydroquinone (a reductant). The results are listed in Table II and show that 39% of the acid-catalyzed reaction of N-nitro-N-methylaniline is intermolecular and 53% of the reaction of *p*-fluoro-N-nitro-N-methylaniline is intermolecular. Furthermore, 39% of all of the *p*-nitro-N-methylaniline formed must arise from an intermolecular pathway.

The above information was used to obtain calculated values in Table I. There is excellent agreement between the experimental and calculated data. Since the assumptions involved in making the computations are derived from the mechanism in Chart I, the close correspondence of these results indicates the essential correctness of this reaction scheme. It is apparent from Table I that no crossover occurs in the presence of hydroquinone. This is in accord with the proposed mechanism since reducing agents destroy the dissociated radicals and eliminate the intermolecular portion of the rearrangement.

Other possible pathways for formation of labeled *p*-nitro-N-methylaniline were excluded by experimental investigation. Chromatography of the reaction product from *p*-fluoro-N-nitro-N-methylaniline and spectrophotometric analysis of the eluate showed that less than 0.16% *p*-nitro-N-methylaniline is formed from the fluoro compound. This amount would increase the ^{15}N content of all of the *p*-nitro-N-methylaniline formed by only 0.1%. It was found that nitrous and nitric acids (which might be formed from the labeled nitramine) did not convert N-methylaniline or N-nitro-N-methylaniline into *p*-nitro-N-methylaniline under rearrangement conditions. Direct transfer of a nitro group from *p*-fluoro-N-nitro-N-methylaniline to N-methylaniline or N-nitro-N-methylaniline is excluded by the finding that nitro-group exchange was eliminated in the concurrent rearrangements when a reducing agent was added. The latter should not affect a direct transfer process. Thus, the only course for crossover of nitro groups is that implied in the mechanism in Chart I.

The rearrangement of N-nitro-N-methylaniline and *p*-fluoro-N-nitro-N-methylaniline and probably other aromatic nitramines are, therefore, partially intermolecular and partially intramolecular. Direct collapse of the caged radicals (formed by N–N bond cleavage in the original nitramine) is the source of the intramolecular component of the reaction while dissociation and later recombination of these same radicals results in the intermolecular portion of the rearrangement.

Experimental Section

***p*-Fluoro-N-nitro(^{15}N)-N-methylaniline.**—A finely ground mixture of 1.584 g of potassium nitrate-^{15}N, 4.0 g of copper powder, and 4.0 g of sodium hydroxide was placed in a test tube and heated at 360° for 1 hr while the test tube was slowly rotated. After cooling, the contents of the tube were leached with about 10 ml of water. The solution was filtered through a sintered glass disk. The filtrate was held at 0° while 25% sulfuric acid solution (about 15 ml) was added to neutralize it. The neutral nitrite solution was poured over a frozen solution of 1.75 g of *p*-fluoroaniline in 12 ml of 15% sulfuric acid solution. The clear solution, which resulted when the mixture was warmed to 0°, was allowed to stand in an ice bath for 15 min. A solution of 32 g of potassium hydroxide and 96 g of potassium ferricyanide in 360 ml of water was added, and the mixture was stirred for 24 hr at room temperature. It was then filtered and the filtrate was washed with 100 ml of ether and subsequently neutralized with acetic acid. The neutral solution was extracted with four 100-ml portions of ether. The combined ether extracts were washed with 40 ml of water and then mixed with 20 ml of water and evaporated at 40°. The resulting oily suspension of nitramine in water was rendered homogeneous by addition of a solution of 40 g of potassium bicarbonate in 140 ml of water. Alkylation with methyl sulfate was carried out as described previously.[9] The product was crystallized from petroleum ether (bp 30–60°) yielding 0.59 g of white crystals, mp 68–69° (lit.[1c] mp 68.6–69.1°).

N-Nitro-N-methylaniline.—This compound, mp 36.8–37.5° (lit.[10] mp 38.5–39.5°), was available from previous investigations.[9]

***p*-Fluoro-N-nitro-N-methylaniline.**—This substance, mp 68.6–69.1°, was also available from earlier studies.[1c]

Concurrent Rearrangement of N-Nitro-N-methylaniline and *p*-Fluoro-N-nitro(^{15}N)-N-methylaniline.—A solution of the appropriate quantities of the two nitramines in 10.0 ml of dioxane was quantitatively transferred to a thermostated (40.0 ± 0.2°) solution of 500.0 ml of 1.022 *M* perchloric acid, 61.28 g (0.500 mol) of sodium perchlorate, 5.0 g of sulfamic acid, and about 450 ml of water contained in a 1-l. volumetric flask. Sufficient water at 40° was added to bring the total volume to 1 l. and the mixture was shaken and kept at 40.0 ± 0.2° for 90 min. The solution was allowed to cool and the pH was adjusted to about 8.5 with sodium hydroxide. The rearrangement product was then extracted with four 100-ml portions of ether, and the combined ether solutions were evaporated. The residue was taken up in 3 ml of carbon tetrachloride and chromatographed on a 26 × 170 mm column of activity grade II neutral alumina using 300 ml of 1:1 diethyl ether–petroleum ether (bp 30–60°) as developer. The *ortho* isomers moved down the column in a single band and were completely eluted by 200 ml of developer. The *para* isomer formed a band 85–125 mm from the top of the column. The column was extruded and the zone containing the *para*

(9) W. N. White, E. F. Wolfarth, J. R. Klink, J. Kindig, C. Hathaway, and D. Lazdins, *J. Org. Chem.*, **26**, 4124 (1961).

(10) E. Bamberger, *Ber.*, **27**, 379 (1894).

isomer was cut out and extracted with 120 ml of ether. The residue obtained by evaporation of the ether solution was recrystallized twice from petroleum ether (bp 30–60°) to give yellow crystals, mp 148–149° (lit.[10] mp 150–151°). The mixture melting point of this substance with an equal quantity of authentic *p*-nitro-N-methylaniline was 149–150°. The chromatographic behavior of the reaction product was also identical with that of *p*-nitro-N-methylaniline.

Determination of Nitrogen-15 Content.—Kjeldahl digestion of the sample converted it into ammonia which was oxidized to nitrogen by hypobromite. The nitrogen was analyzed by mass spectrometry.[11] In the Kjeldahl procedure, excess glucose was added to the potassium sulfate–sulfuric acid digestion mixture, and it was cooled to 0° before addition of the sample to avoid the loss of nitrogen oxides. Titration of an aliquot of the distillate indicated that conversion of organically bound nitrogen to ammonia was complete in each case. Methylamine was shown to be absent by gas chromatography.

The ammonium ion in the distillate was converted into nitrogen by oxidation with sodium hypobromite which contained 0.1% sodium iodide. The nitrogen was then analyzed by mass spectrometry.

Spectrophotometric Analysis of the Rearrangement Products of N-Nitro-N-methylaniline and *p*-Fluoro-N-nitro-N-methylaniline.—The previously described procedure[1a,c] was utilized. However, the reaction mixtures were made up somewhat differently: 25.0 ml of 1.022 *M* perchloric acid, 3.061 g (0.025 mol) of sodium perchlorate, 0.25 g of sulfamic acid, and about 20 ml of water was thermostated at 40.0 ± 0.2° before the addition of 2.0 ml of a dioxane solution of the sample and enough water to bring the volume to 50.0 ml. The presence of sulfamic acid in the reaction mixture obviated the necessity of heating aliquots of the latter with sulfamic acid solution before diluting with buffer.

Kinetic Measurements.—Rate constants for rearrangement of the two nitramines were determined spectrophotometrically.[1b,c] The reaction mixtures were made up as described in the previous paragraph.

Chromatographic Analysis of Rearrangement Product of *p*-Fluoro-N-nitro-methylaniline.—The concurrent rearrangement procedure described above was utilized with *p*-fluoro-N-nitro-N-methylaniline alone being added to the reaction mixture. The chromatographic eluate containing the *ortho* isomer was evaporated, and the residue was diluted with 95% ethanol to a concentration convenient to measure. The column was extruded and the central portion which should contain any *p*-nitro-N-methylaniline formed was cut out and extracted with ether. The residue from evaporation of the ether solution was also dissolved in a convenient amount of 95% ethanol. The absorbances of these two ethanol solutions at 370, 390, 410, and 430 mμ were determined. By comparing these with the absorbances of standard solutions of 2-nitro-4-fluoro-N-methylaniline and *p*-nitro-N-methylaniline in 95% ethanol, it was possible to compute the yields of these two compounds from the rearrangement: 77.2 ± 0.7% of the former and 0.16 ± 0.10% of the latter.

A synthetic mixture containing 1.31% *p*-nitro-N-methylaniline and 98.69% 2-nitro-4-fluoro-N-methylaniline was subjected to the same rearrangement conditions, separated chromatographically, and analyzed spectrophotometrically. The assay indicated that the mixture consisted of 1.37 ± 0.1% *p*-nitro-N-methylaniline and 94.3 ± 0.4% of 2-nitro-4-fluoro-N-methylaniline.

Reaction of N-Methylaniline with Nitrous Acid and Nitric Acid.—A 1.00-ml aliquot of 0.10 *M* sodium nitrite solution was added to a thermostated (40.0 ± 0.2°) solution of 25.0 ml of 1.022 *M* perchloric acid, 3.061 g (0.025 mol) of sodium perchlorate, 2.00 ml of 0.025 *M* N-methylaniline, and about 20 ml of water. Enough water at 40° was added to bring the volume to 50.0 ml, and the mixture was shaken and then kept at 40.0 ± 0.2° for 90 min. The solution was cooled and a 5.0-ml aliquot was heated with 5.0 ml of 5% ammonium sulfamate solution and then analyzed for *o*- and *p*-nitro-N-methylaniline as previously described.[1a] Not more than 0.21 ± 0.11% of the *ortho* isomer and 0.14 ± 0.09% of the *para* isomer were detected.

Substitution of 0.10 *M* sodium nitrate solution for the sodium nitrite resulted in not more than 0.16 ± 0.08% of the *ortho* isomer and 0.08 ± 0.10% of the *para* isomer.

Registry No.—*p*-Fluoro-N-nitro(^{15}N)-N-methylaniline, 24454-09-9; N-nitro-N-methylaniline, 7119-93-9; *p*-fluoro-N-nitro-N-methylaniline, 655-56-1; *p*-nitro-N-methylaniline, 100-15-2.

(11) D. Rittenberg in D. W. Wilson, A. O. C. Nier, and S. P. Riemann, "Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Mich., 1948, p 31.

Electron Acceptors Derived from Fluorenecarboxylic Acids and Their Charge-Transfer Complexes

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Fluorenone-2,7-dicarboxylic acid (XII) and fluorenone-2-carboxylic acid (XVI) and -4-carboxylic acid (XIX) have been nitrated to give 4,5-dinitrofluorenone-2,7-dicarboxylic acid (Va), 4,5,7-trinitrofluorenone-2-carboxylic acid (XVII), and 2,5,7-trinitrofluorenone-4-carboxylic acid (XX), respectively. Reaction of these acids, or the corresponding methyl esters, with malononitrile in the presence of piperidine gave the 9-dicyanomethylene derivatives. These compounds, which represent a new class of functionalized electron acceptors, readily formed charge-transfer complexes with aromatic hydrocarbons and aromatic monoamines. With N,N,N′,N′-tetramethyl-*p*-phenylenediamine, the radical anions and cations were formed exclusively. By use of simple molecular orbital theory, it was shown that these compounds have acceptor strengths similar to chloranil.

Charge-transfer complexes have been studied by many workers from various viewpoints. Their research has been described in several reviews.[1] Until recently, this work was limited to the interactions of monomeric electron donors and electron acceptors. Because of active interest in preparing practical organic semiconductors, these studies were extended to include donor polymer–acceptor monomer complexes.[2] Interactions between polymers containing donor substituents with polymers containing acceptor groups were recently reported for the first time.[3] The donor polymers were prepared from aryliminodiethanols and the acceptor polymers from nitrated isophthalic and terephthalic acids. We found, however, that, while the donors

(1) (a) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964. (b) E. M. Kosower, *Progr. Phys. Org. Chem.*, **3**, 81 (1965). (c) F. E. Gutmann and L. E. Lyons, "Organic Semiconductors" John Wiley & Sons, Inc., New York, N. Y., 1967.

(2) (a) W. Slough, *Trans. Faraday Soc.* **158**, 2360 (1962); British Patent 1,009,361 (Nov 10, 1965). (b) J. H. Lupinski and K. D. Kopple, *Science*, **146**, 1038 (1964); U. S. Patent 3,346,444 (Oct 10, 1967).

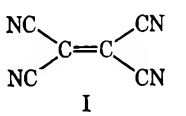
(3) (a) T. Sulzberg and R. J. Cotter, *Macromolecules*, **1**, 554 (1968). (b) *ibid.*, **2**, 146 (1969). (c) *Chem. Eng. News*, **46** (54), 28 (1968).

were electron rich and readily formed strong charge transfer complexes, the acceptor polymers only formed weak complexes.

In order to prepare more powerful acceptor polymers, a species of much higher electron affinity than the nitrated phthalic acids should be constructed. Further, since one goal was the synthesis of tough, soluble, and well-defined polymers, research was concentrated on condensation polymers.[3]

A functional group that has been studied extensively to prepare acceptors of high electron affinity is the dicyanomethylene group.[4] Some compounds, such as tetracyanoethylene (I),[4a] tetracyanoquinodimethane (II),[4b] 2-dicyanomethylene 1,3-indanedione (III),[4c] and 9-dicyanomethylene-2,4,7-trinitrofluorene (IV),[4d,e] are readily prepared and have been characterized as being excellent electron acceptors. Therefore, we chose IV as a model on which to base our synthetic studies of new, functionalized electron acceptors.

This paper reports the synthesis and study of a series of functionalized fluorene acceptors (V–IX) for use in the synthesis of condensation polymers.



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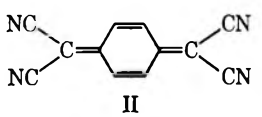

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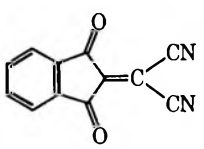

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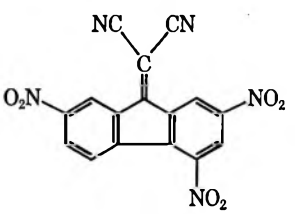
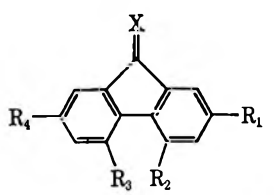
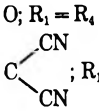


IV



V, X = O; $R_1 = R_4$ = COY and $R_2 = R_3 = NO_2$

VI, X =  ; $R_1 = R_4$ = COY and $R_2 = R_3$ = H

VII, X =  ; $R_1 = R_4$ = COY and $R_2 = R_3 = NO_2$

VIII, X =  ; R_1 = COY and $R_2 = R_3 = R_4 = NO_2$

IX, X =  ; R_2 = COY and $R_1 = R_3 = R_4 = NO_2$

and Y is (a) OH, (b) Cl, and (c) OCH_3

Results and Discussion

Synthesis.—The synthesis of acceptors based on fluorenone-2,7-dicarboxylic acid (XII) as a key intermediate is presented in Scheme I. Several methods were evaluated to diacetylate fluorene to XI. Adding acetyl chloride to a solution of fluorene and aluminum chloride in either carbon disulfide[5] or in methylene chloride was one variation. The reverse method of adding aluminum chloride to the other reactants was also tried. The purest product was obtained by adding a 1,2-dichlorethane solution of the acetic anhydride–aluminum chloride complex to a solution of fluorene in 1,2-dichloroethane.[6] Subsequent heating and work-up gave 60% yields of pure XI.

The use of sodium dichromate to oxidize XI to XII was attempted but it gave poor yields (<30%) because of the difficulty in separating XII from the resulting chromium salts.[7] While sodium hypochlorite prepared *in situ* gave <20% yields of XII, commercially available "Clorox" solutions gave 95% yields.

Conversion of XII to the diacid chloride (XIII) was performed routinely using an excess of thionyl chloride and N,N-dimethylformamide as catalyst.[7] While the keto diester (XIV) was prepared from either XII or XIII, reaction of XII with methanol and sulfuric acid was preferred.[7] The infrared spectra of compounds XII–XIV are discussed below.

The nitration of XII to yield Va was accomplished with a combination of fuming nitric acid and fuming sulfuric acid. A similar procedure was used to convert fluorenone to 2,4,5,7-tetranitrofluorenone.[8] Since the yields of Va were as high as 70%, alternate methods were not tried. Esterification of acid Va to Vc was done routinely with methanol–sulfuric acid.

The conversion of the various substituted 9-fluorenones (Va, Vc, XII, and XIV) to the corresponding 9-dicyanomethylene derivatives was carried out by two procedures. First, the compounds were slurried in methanol and malononitrile, piperidine was added, and then the reaction mixture was heated under reflux.[4a] Even though the reaction appears to occur heterogeneously, the reactants and products must possess slight solubility in methanol.

The second method for converting fluorenones to their dicyanomethylene derivatives used dimethyl sulfoxide as the reaction medium. The starting materials were dissolved in this solvent and the solution was heated to 120–130°. Since the products were very soluble in dimethyl sulfoxide, cooling in an ice bath was needed to precipitate them.

Finally, VIIa was converted to VIIc with thionyl chloride without the use of DMF. The latter complexes with VIIa and VIIc and was difficult to remove.

The procedures used to synthesize the two series of fluorene monocarboxylic acids are presented in Scheme II. Since these methods are very similar to those described above for the preparation of the fluorene-2,7-dicarboxylic acid acceptors, only the procedural differences will be discussed in detail. The use of crude XV for conversion to XVI probably accounts for the low yield (21%) that was attained. The synthesis of XVI was previously reported by the sodium dichromate oxi-

(4) (a) R. E. Merrifield and W. D. Phillips, *J. Amer. Chem. Soc.*, **80**, 2778 (1958). (b) L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *ibid.*, **84**, 3374 (1962). (c) S. Chatterjee, *Science*, **157**, 314 (1967). (d) H. D. Hartzler, U. S. Patent 3,226,388 (Dec 28, 1965) to Du Pont. (e) T. K. Mukherjee and L. A. Levasseur, *J. Org. Chem.*, **30**, 644 (1965).

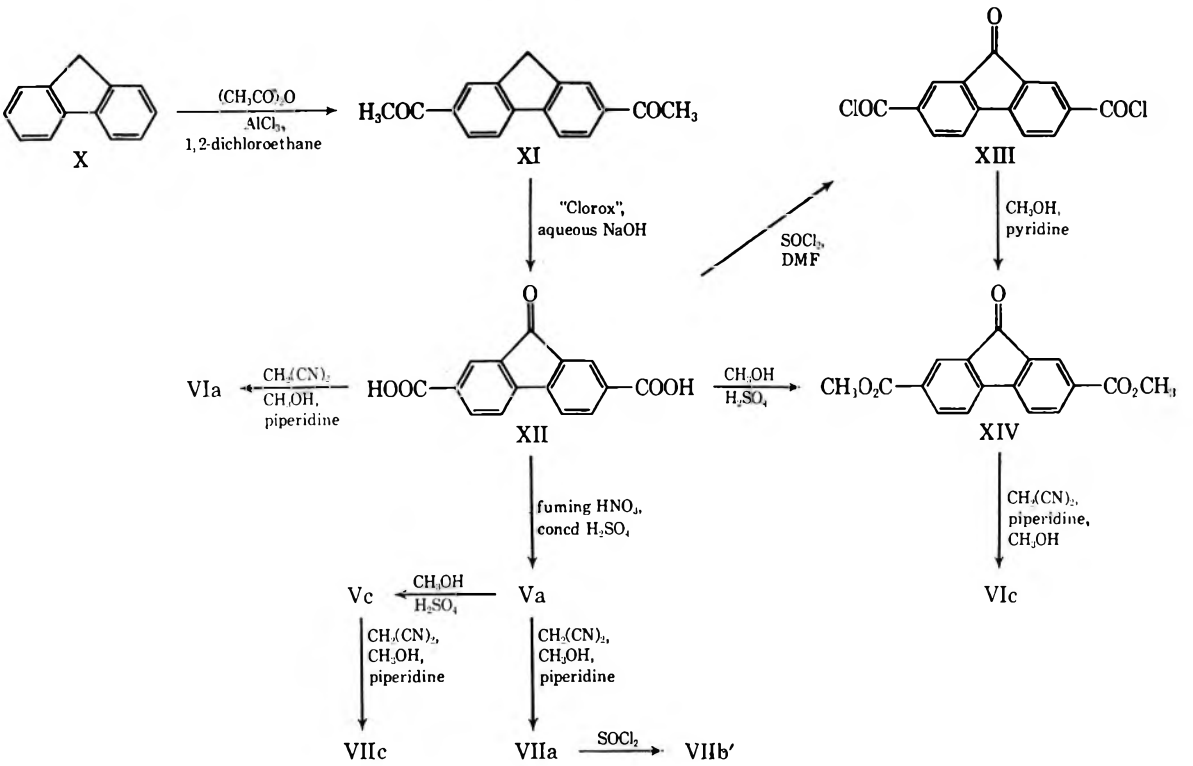
(5) K. Dziewonski and J. Schnayder, *Bull. Int. Acad. Pol. Sci. Lett. Cl. Math. Natur.*, 529 (1930).

(6) M. M. Dashenskii and E. M. Shamis, *Ukr. Khim Zh.*, **30** (9), 938 (1964).

(7) (a) K. Dziewonski, St. Kuzdrol, and J. Mayer, *Bull. Int. Acad. Pol. Sci. Lett. Cl. Math. Natur.*, 348 (1934). (b) N. Ishikowa and T. Ozawa, *Yûki Gôsei Kogaku Kyokai Shi*, **17**, 553 (1959); *Chem. Abstr.*, **54**, 540*f* (1960).

(8) M. S. Newman and H. Boden, *Org. Syn.*, **42**, 95 (1962).

SCHEME I
FLUORENE-2,7-DICARBOXYLIC ACID ACCEPTORS



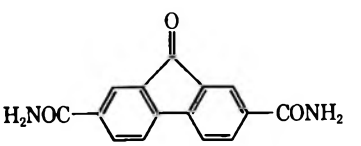
dation of XV.[9] Nitration of XVI to XVII proceeded in high yield (85%) because of the solubility of XVI in sulfuric acid. The subsequent conversions to XVIII and VIIIc and to VIIIa and VIIIb were performed as discussed above. Again, the nitration, esterification, dicyanomethylations and acid chloride formations were carried out in a similar manner to those discussed above.

Infrared Spectra.—In the initial synthesis of the keto diester XIV, a single very strong carbonyl absorption band was observed at 5.81 μ (see Table I).

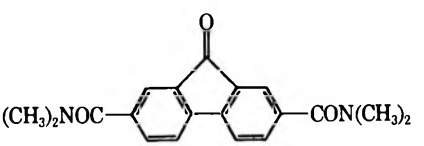
TABLE I
CARBONYL STRETCHING BANDS OF DISUBSTITUTED FLUORENONE DERIVATIVES

Compd	Carbonyl bands and comments, μ
XII	5.79, 5.85, 5.90, and 5.95 (equal intensities)
XIII	5.73 (sharp)
	5.82 (shoulder)
XIV	5.81 (very sharp)
XXII	5.90 (6.05, very broad)
XXIII	5.82 (sharp, ketone band)
	6.14 (tertiary amide band)

Though XIV is a known compound some questions arose as to its structure.[7a] The infrared spectra of two precursors (XII and XIII) seemed consistent with their structures, but for confirmatory evidence fluorenone-2,7-dicarboxamide (XXII) was prepared from XIII and ammonia.[7a] Unfortunately, the keto group was completely masked by being hydrogen bonded and one very broad carbonyl band appeared at 5.90–6.05 μ. Finally, the reaction of dimethylamine and XIII gave the crude N,N,N′,N′-tetramethylfluorenone-2,7-dicarboxamide (XXIII). This compound had a sharp



XXII



XXIII

ketone band at 5.82 μ and a tertiary amide carbonyl band at 6.14 μ. This provided the conclusive proof of the position of the ketone carbonyl band in XIV.

Charge-Transfer Complexes and Spectra. A. With Aromatic Hydrocarbons.—As a means of determining the electron acceptor characteristics of the various fluorene compounds, a study of their complexes with aromatic hydrocarbons, aromatic monoamines, and aromatic diamines was undertaken.

The acceptor strength of compounds can be determined by a method described by Dewar and coworkers.[10] The method is based on simple molecular orbital theory which states that the spectrum of a charge-transfer complex arises from an electronic transition from the highest occupied molecular orbital of the donor to the lowest vacant molecular orbital of the acceptor. Simply, if the acceptor is kept constant in a

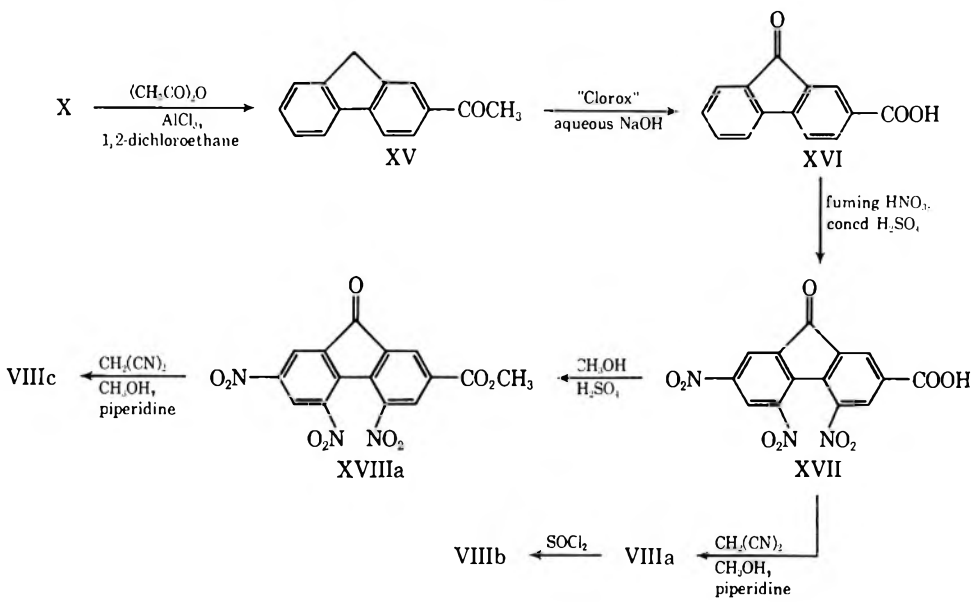
(9) G. Rieveschl, Jr., and F. E. Ray, "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 420.

(10) (a) M. J. S. Dewar and A. R. Lepley, *J. Amer. Chem. Soc.*, **83**, 4560 (1961); (b) M. J. S. Dewar and H. Rogers, *ibid.*, **84**, 395 (1962).

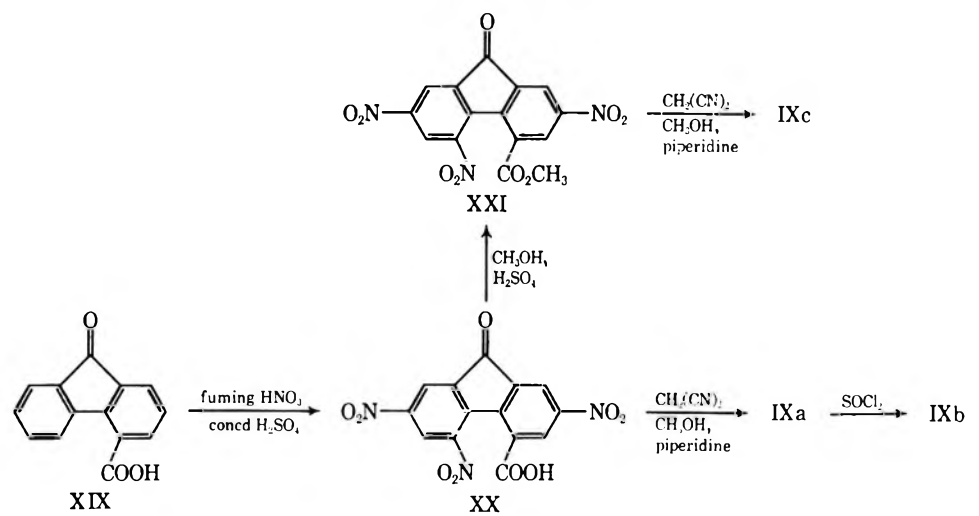
SCHEME II

FLUORENE MONOCARBOXYLIC ACID ACCEPTORS

A. Fluorene-2-carboxylic Acid



B. Fluorene-4-carboxylic Acid



series of complexes with different donors one derives the expression

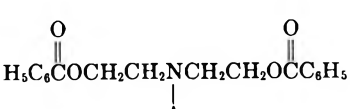
$$\Delta E = \text{constant} - n\beta$$

where ΔE is the energy of the charge-transfer transition, β is the resonance integral, and n is the coefficient of β.

Since ΔE is proportional to spectral frequency, a plot of the observed charge transfer frequency against calculated n values[11] of the donors gives a straight line. Further, the y intercept of the line represents the energy level of the acceptor's lowest vacant molecular orbital (n value for acceptor) and a comparison of these values for various acceptors leads to a list of relative strengths.

The charge-transfer spectral absorption maxima of compounds Vc, VIc, VIIc, VIIIc, and IXc with a group of donor hydrocarbons are given in Table II. Also included are the published values for IV, 2,4,7-trinitrofluorenone (TNF), and tetracyanoethylene (TCNE). By plotting $1/\lambda$ (frequency of the charge-transfer absorption) against the molecular orbital coefficient (n) and determining the y intercepts for each compound, the relative acceptor abilities shown in Table III were obtained. The data indicates that the four dicyanomethylene fluorenes (IV, VIIc, VIIIc, and IXc) are of approximately equal acceptor strength, falling between TCNE and TNF. They appear to be quite similar in acceptor strength to chloranil.

B. With Aromatic Monoamines.—As model compounds for donor polymers,[3] dibenzoates XXIV and XXV were prepared. The charge transfer spectra



XXIV, Ar = phenyl
XXV, Ar = p-anisyl

of these amines with several acceptors were determined and are given in Table IV. These data confirm the

(11) C. A. Coulson and R. Daudel, "Dictionary of Values of Molecular Constants," 2nd ed, Centre de Chemie Théorique de France, Paris, France, 1959.

TABLE II

CHARGE-TRANSFER SPECTRA FOR HYDROCARBON–ACCEPTOR COMPLEXES[a]

Donor	n[b]	IVc[c]	Vc	VIc	VIIc	VIIIc	IXc	TNF[d]	TCNE[e]
Fluorene	0.635	523	...[g]	450	517	537	525	425	...[h]
Anthracene	0.414	662	500	540	662	685	670	541	740
3,4-Benzopyrene	0.371	726	570	580	718	725	730	590	820
1,2,5,6-Dibenzanthracene	0.473	...[f]	500	515	...[f]	...[f]	590	...[f]	635
Perylene	0.347	745	600	610	790	790	785	620	920
Pyrene	0.445	650	500	535	644	670	645	520	720
Phenanthrene	0.605	500	...[g]	431	497	504	517	435	540
1,2-Benzanthracene	0.452	640	...[g]	...[g]	620	650	623	522	748
1,2-Benzoperylene	0.439	675	...[g]	...[g]	695	670	693	570	812
Triphenylene	0.684	508	...[g]	...[g]	508	535	533	425	570
Acenaphthylene	0.637	550	...[g]	...[g]	487	530	487	415	502

[a] Spectra of donors with acceptors run in 1,1,2,2-tetrachlorethane solution on a Cary 14 spectrophotometer. Data are presented in millimicrons (mμ). [b] The *n* values describe the donor ability of the aromatic hydrocarbons. These are calculated (lit.[11]) and the lower numbers indicate larger π electron availability. [c] See reference 4e. [d] Data for TNF from reference 4e. [e] Data for TCNE from reference 10b. [f] Several of the complexes of 1,2,5,6-dibenzanthracene were too insoluble and no spectral data was obtained. [g] Vc and VIc gave complexes which absorbed at low wavelengths with weak intensities and a further study was not made. [h] Not reported.

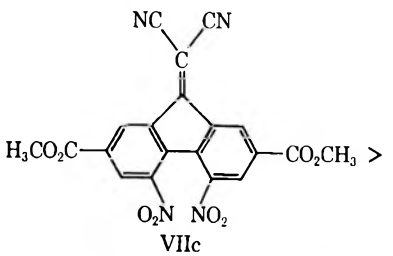
TABLE III

RELATIVE STRENGTHS OF CHARGE-TRANSFER ACCEPTORS

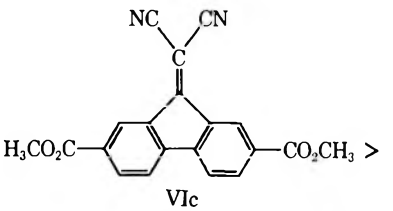
Compd	n[e]
TCNE[a]	−0.11
VIIc	−0.20
IV	−0.21
Chloranil[b]	−0.22
IXc	−0.25
VIIIc	−0.26
TNF[c]	−0.30
VIc	−0.38
Vc	−0.40
1,3,5-Trinitrobenzene[d]	−0.46

[a] See M. J. S. Dewar and H. Rogers, *J. Amer. Chem. Soc.*, **84**, 395 (1962). [b] Calculated from data of G. Briegleb, "Elektronen-Donator-Acceptor-Komplexe," Springer-Verlag, Berlin 1961. [c] See A. R. Lepley, *J. Amer. Chem. Soc.*, **84**, 3577 (1962). [d] See S. Chatterjee, *J. Chem. Soc. B*, 1170 (1967). [e] Just as *n* values represent donor abilities of electron rich systems, −*n* values are a measure of ease of electron acceptor strength. The better the acceptor, the higher its *n* value.

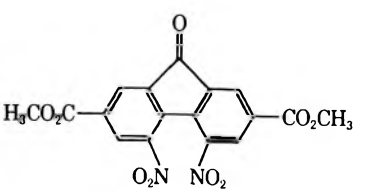
previous evidence that the order of acceptor strength is as follows



VIIc



VIc



Vc

TABLE IV

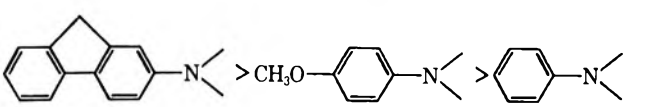
CHARGE-TRANSFER SPECTRA OF TERTIARY AMINE–ACCEPTOR COMPLEXES[a]

	Amine monomers		Amine polymers		
Acceptor	XXIV	XXV	...[b]	...[c]	...[d]
VIIc	662	800	640	760	800
VIc	530	620	530	600	630
Vc	<500	500			
DDQ	940	>1050			
Chloranil	670	795	535	735	740

[a] Spectra run in 1,1,2,2-tetrachloroethane on a Cary 14. Spectrophotometric data are presented in mμ. [b] Poly(phenyliminodiethanol–bisphenol A carbonate). [c] Poly(*p*-anisyliminodiethanol–bisphenol A carbonate). [d] Poly(2-fluorenyliminodiethanol–bisphenol A carbonate).

Further, it shows that VIIc is not so strong an acceptor as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) but, as previously shown, it is about equal to chloranil.

C. With Donor Polymers.—The charge-transfer spectra of several donor polymer–acceptor monomer mixtures are given in Table IV. The predicted order of donor ability is demonstrated, *i.e.*



2-fluorenylimino *p*-anisylimino phenylimino

Of further interest is the comparison of the data for the monomeric and polymeric amines. Using the same acceptor (VIIc), the monomeric phenylimino and *p*-anisylimino compounds absorb at higher wavelengths, 662 and 800 mμ, as compared with 640 and 760 mμ for the polymeric species. With chloranil, this effect is equally pronounced. The same is true, although to a lesser degree, with acceptor VIc. These data indicate that the acceptors form complexes of lower spectral transition energy with the monomeric donors than with less the mobile, donor polymer chains.

D. With Aromatic Diamines. Radical-Ion Formation.—It was shown above (Table IV) that the complex between VIIc and XXIV absorbed at 662 mμ. The addition of a *p*-methoxyl group in the donor caused the spectral maximum to shift to 800 mμ or a change of 138 mμ. If the more powerful dimethylamino group was used, an even longer wavelength absorption would be anticipated. In Table V is the data obtained from

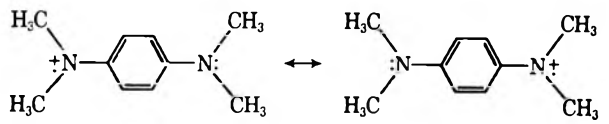
TABLE V

VISIBLE SPECTRA OF TMPD WITH ACCEPTORS[a,b]

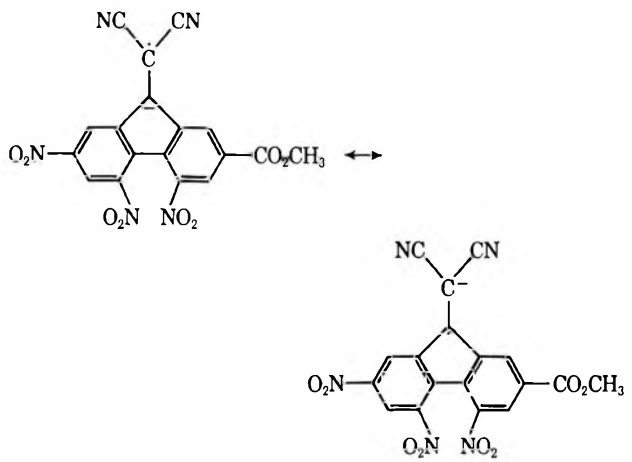
Acceptor	λ_{max}, mμ	Comments
	570	Purified TMPD
	620	Very weak owing to radical cation *via* air oxidation
VIIIc	567	Strong peaks (radical cation)
	620	
	745	Radical anion
IXc	570	Strong peaks (radical cation)
	620	
	750	Radical anion
IV[c]	740	No amine used; acceptor + LiI → radical anion

[a] Spectra run in 1,1,2,2-tetrachloroethane on a Cary 14 spectrophotometer. [b] The reported absorptions for the TMPD cation-radical are 570 and 620 mμ (see reference 12). [c] See reference 4e.

mixing VIIIc and IXc with N,N,N′,N′-tetramethyl-*p*-phenylenediamine (TMPD). The mixtures each have three absorption peaks at wavelengths below those previously discussed. The 570- and 620-mμ peaks are directly attributable to the radical cation of TMPD.[12]



The absorptions in the 740–750-mμ region are assigned to the radical anion of the α-dicyanomethylene fluorene species.[4e]



Experimental Section

2,7-Diacetylfluorene (XI).—To an ice-cooled mixture of 400 g (3 mol) of aluminum chloride and 500 ml of anhydrous 1,2-dichloroethane, acetic anhydride (153 g; 1.5 mol) was added dropwise with stirring. The addition time was 1.5 hr. The gray-green solution was added dropwise to 73 g (0.44 mol) of fluorene in 500 ml of 1,2-dichloroethane at 25°. After the addition, the reaction mixture was refluxed for 1.5 hr while 500 ml of 1,2-dichloroethane was distilled off. After pouring onto ice–HCl, the aqueous phase was decanted. The remainder was dissolved in 2 l. of hot acetone, cooled in the cold room and the solid collected. The 2,7-diacetylfluorene (77 g) which melted at 178–9° (lit.[5] mp 181–183°) was obtained in 62% yield.

Fluorenone-2,7-dicarboxylic Acid (XII).—A mixture of 76 g (0.3 mol) of 2,7-diacetylfluorene, 3 l. of "Clorox" (5.25% sodium hypochlorite), and 15 g of sodium hydroxide was heated slowly to about 65°. The reaction, which became exothermic, was kept below 80°. Periodic testing of the solution with pH paper was done to keep it alkaline (pH >10). Adding small increments of sodium hydroxide ensured its basicity. After 4 hr, little solid was left floating in the solution and the reaction mixture was filtered to give 3.5 g of recovered 2,7-diacetylfluorene. After the excess sodium hypochlorite in the filtrate was destroyed with sodium hyposulfite, concentrated hydrochloric acid was added to obtain a pH of 3. The resulting yellow solid was collected, boiled in water for 0.5 hr, collected, and dried at 100° (1 mm). The yield of fluorenone-2,7-dicarboxylic acid was 77.2 g (94.7%) and the conversion was 99.4%. It appeared to melt with decomposition at 400° (reported 407°).[5]

Fluorenone-2,7-dicarboxylic Acid Chloride (XIII).—A mixture of 2.0 g (6.6×10^{-3} mol) of fluorenone-2,7-dicarboxylic acid, 25 ml of thionyl chloride and 1 ml of N,N-dimethylformamide was refluxed for 18 hr. After stripping the solvent, there was 1.5 g (70%) of solid. Recrystallization from toluene gave the acid chloride, mp 197–199° (lit.[7b] mp 198–200°).

Dimethyl Fluorenone-2,7-dicarboxylate (XIV).—A slurry of 10 g (3.8×10^{-2} mol) of fluorenone-2,7-dicarboxylic acid in 200 ml of methanol and 20 ml of concentrated sulfuric acid was refluxed for 20 hr. The resulting yellow solid was collected, washed with water and dried. The dimethylfluorenone-2,7-dicarboxylate, which was recrystallized from acetic acid and melted at 217–218° (lit.[7a] mp 218°), was obtained in 85% yield (9.5 g): nmr (CF_3COOH) δ 8.30 (doublet of doublet, 2, J = 1.4 and 8.2 Hz, aromatic protons in 3 and 6 positions), 8.09 (d, 2, J = 1.4 Hz, aromatic protons in 1 and 8 positions), 7.62 (d, 2, J = 8.2 Hz, aromatic protons in 4 and 5 positions), and 4.15 (s, 6, $-OCH_3$).

Anal. Calcd for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08; O, 27.00. Found: C, 68.99; H, 4.00; N, 27.01.

The diester was also prepared from fluorenone-2,7-dicarboxylic acid chloride, methanol and pyridine. The infrared spectrum showed only a single sharp carbonyl band at 5.81 μ.

4,5-Dinitrofluorenone-2,7-dicarboxylic Acid (Va).—A heated solution of 5.4 g (2×10^{-2} mol) of fluorenone-2,7-dicarboxylic acid in 40 ml of concentrated sulfuric acid, which was a deep red, was added dropwise over a 10-min period to a refluxing mixture (85°) of 65 ml of fuming nitric acid and 40 ml of concentrated sulfuric acid. A mixture of 45 ml of fuming nitric acid and 55 ml of concentrated sulfuric acid was added dropwise over a 4.5-hr period. The reaction, which was cooled to room temperature and stirred overnight, was poured onto 1 l. of ice water to give a pale yellow solid. It was collected, water washed and dried at 70° (1 mm). The 4,5-dinitrofluorenone-2,7-dicarboxylic acid (5.2 g, 72%) had a melting range of 285–294° dec.

Anal. Calcd for $C_{15}H_6N_2O_9$: C, 50.29; H, 1.69; N, 7.82; O, 40.20. Found: C, 48.44; H, 2.23; N, 8.77; O, 40.58.

Dimethyl 4,5-Dinitrofluorenone-2,7-dicarboxylate (Vc).—A mixture of 3.0 g (8.4×10^{-3} mol) of 4,5-dinitrofluorenone-2,7-dicarboxylic acid, 61 ml of concentrated sulfuric acid and 60 ml of methanol was heated at reflux for 18 hr. The solution was cooled, the solid filtered, washed with water and dried to give 2.1 g (66%) of Vc. After recrystallization from toluene–ethanol it melted at 252–255°: nmr (CF_3COOH) δ 9.92 (d, 2, J = 1.4 Hz, aromatic protons in 3 and 6 positions), 9.80 (d, 2, J = 1.4 Hz, aromatic protons in 1 and 8 positions) and 4.37 (s, 6, $-OCH_3$).

Anal. Calcd for $C_{17}H_{10}N_2O_9$: C, 52.86; H, 2.61; N, 7.25; O, 37.28. Found: C, 52.30; H, 2.54; N, 8.16; O, 37.20.

9-Dicyanomethylenefluorene-2,7-dicarboxylic Acid (VIa).—A mixture 2.7 g (1×10^{-2} mol) of fluorenone-2,7-dicarboxylic acid and 250 ml of methanol was heated to reflux. Malononitrile (2.0 g, 3×10^{-2} mol) and 2 drops of piperidine were added. The slurry turned from yellow to orange during 17 hr at reflux. The reaction mixture was cooled and the solid filtered. The product, which melted at 312–316°, was collected in 68% yield (2.15 g).

Anal. Calcd for $C_{18}H_8N_2O_4$: C, 68.36; H, 2.55; O, 8.86; O, 20.23. Found: C, 69.45; H, 2.88; N, 8.46; O, 17.25.

Dimethyl-9-dicyanomethylenefluorene-2,7-dicarboxylate (VIc).—Dimethylfluorenone-2,7-dicarboxylate (3.0 g, 1×10^{-2} mol) and 250 ml of methanol were heated to reflux. Malononitrile (2.0 g, 3×10^{-2} mol) and 2 drops of piperidine was added and heating continued for 1 hr. The reaction mixture was cooled, the orange solid collected and recrystallized from acetonitrile–dimethylformamide to give 2.5 g (74%) of product melting at 275–8°. An infrared spectrum had a cyano band at 4.48 μ.

Anal. Calcd for $C_{20}H_{12}N_2O_4$: C, 69.77; H, 3.51; N, 8.14; O, 18.58. Found: C, 69.59; H, 3.63; N, 8.05; O, 18.89.

(12) R. Foster and T. J. Thomson, *Trans. Faraday Soc.*, **58**, 860 (1962).

Dimethyl 9-dicyanomethylenefluorene-2,7-dicarboxylate was also prepared in 76% yield by using dimethyl sulfoxide as solvent at 130° for 18 hr. Unlike the methanol procedure, the product was soluble in the solvent and ice bath cooling was required to obtain the product. This procedure was more useful for larger quantities than the above method.

4,5-Dinitro-9-dicyanomethylenefluorene-2,7-dicarboxylic Acid (VIIa).—After a mixture of 14.4 g (4×10^{-2} mol) of 4,5-dinitrofluorenone-2,7-dicarboxylic acid and 400 ml of methanol was heated to reflux, 8.0 g (0.12 mol) of malononitrile and 8 drops of piperidine were added. After 1.5 hr at reflux, the solution was cooled in the cold room and 5.4 g (33%) of an orange solid was collected, mp 345°.

Anal. Calcd for $C_{18}H_6N_4O_8$: C, 53.22; H, 1.49; N, 13.79; O, 31.50. Found: C, 53.19; H, 1.55; N, 13.81; O, 31.38.

4,5-Dinitro-9-dicyanomethylenefluorene-2,7-dicarboxylic Acid Chloride (VIIb).—4,5-Dinitro-9-dicyanomethylenefluorene-2,7-dicarboxylic acid (1.6 g; 5×10^{-3} mol) and 25 ml of thionyl chloride were heated at reflux for 5 hr. The excess thionyl chloride was removed by distillation and the residue recrystallized from toluene to give 1.5 g (84%) of diacid chloride, mp 262–264°.

Anal. Calcd for $C_{18}H_4Cl_2N_4O_6$: C, 48.79; H, 0.91; Cl, 15.99; N, 12.64; O, 21.66. Found: C, 48.75; H, 1.22; Cl, 15.73; N, 12.48; O, 21.76.

Dimethyl 4,5-Dinitro-9-dicyanomethylenefluorene-2,7-dicarboxylate (VIIc).—Dimethyl 4,5-dinitrofluorenone-2,7-dicarboxylate (3.0 g; 7.8×10^{-3} mol) and 200 ml of methanol were heated to reflux. Malononitrile (1.4 g, 2.1×10^{-2} mol) and 3 drops of piperidine were added and the solution changed from orange to red-purple. After refluxing for 2 days, the solution was cooled and the deep orange solid collected. The dimethyl 4,5-dinitro-9-dicyanomethylenefluorene-2,7-dicarboxylate (1.8 g, 53%) melted at 280–281° on recrystallization from acetonitrile.

Anal. Calcd for $C_{20}H_{10}N_4O_8$: C, 55.31; H, 2.32; N, 12.90; O, 29.47. Found: C, 55.19; H, 2.36; N, 12.89; O, 29.30.

2-Acetylfluorene (XV).—To an ice-cooled mixture of 135 g (1 mol) of aluminum chloride and 200 ml of anhydrous 1,2-dichloroethane, acetic anhydride (51 g, 0.5 mol) was added dropwise with stirring. The addition time was 1 hr. The gray-green solution was added dropwise to 83 g (0.5 mol) of fluorene in 150 ml of 1,2-dichloroethane at 25°. After the addition, the reaction mixture was refluxed for 1.5 hr while 200 ml of 1,2-dichloroethane was distilled off. The solution was poured onto ice–HCl and then warmed on the steam bath to remove the 1,2-dichloroethane. The resulting solid weighed 104 g (100% yield) and was oxidized without further purification to fluorenone-2-earboxylic acid.

Fluorenone-2-carboxylic Acid (XVI).—A mixture of 104 g (0.5 mol) of crude 2-acetylfluorene, 3 l. of "Clorox," and 15 g of sodium hydroxide were treated as described above for the preparation of fluorenone-2,7-dicarboxylic acid. There was obtained 24 g (21%) of fluorenone-2-carboxylic acid, mp ~335°C (lit.[7b] 340°).

4,5,7-Trinitrofluorenone-2-carboxylic Acid (XVII).—A solution of 10 g (4×10^{-2} mol) of fluorenone-2-carboxylic acid in 80 ml of concentrated sulfuric acid, which was red in color, was added dropwise over a 10 minute period to a refluxing mixture (85°) of 130 ml of fuming nitric acid and 80 ml of concentrated sulfuric acid. A mixture of 90 ml of fuming nitric acid and 110 ml of concentrated sulfuric acid was added dropwise over a 4.5 hr period. After cooling to room temperature, the reaction mixture was stirred overnight, poured onto 1.5 l. of ice water and the yellow solid collected. After washing with a 5% sodium bicarbonate solution and water, the solid was dried overnight at 90° *in vacuo*. This afforded 12.2 g (85%) of 4,5,7-trinitrofluorenone-2-carboxylic acid melting at 267–275°.

Anal. Calcd for $C_{14}H_5N_3O_9$: C, 46.81; H, 1.40; N, 11.70; O, 40.09. Found: C, 46.79; H, 1.76; N, 11.61; O, 39.80.

Methyl 4,5,7-Trinitrofluorenone-2-carboxylate (XVIII).—A mixture of 4.0 g (1.1×10^{-2} mol) of 4,5,7-trinitrofluorenone-2-carboxylic acid, 200 ml of dry methanol and 5 ml of concentrated sulfuric acid was refluxed for 24 hr. The solution was cooled to afford 2.8 g (68%) of the yellow, crystalline methyl 4,5,7-trinitrofluorenone-2-carboxylate: mp 175–8°; nmr (DMSO-d_6) δ 8.97 (d, 1, J = 2.2 Hz, aromatic proton in 6 position), 8.72 (d, 1, J = 2.2 Hz, aromatic proton in 8 position), 8.67 (d, 1, J = 1.6 Hz, aromatic proton in 3 position), 8.51 (d, 1, J = 1.6 Hz, aromatic proton in 1 position), and 4.02 (s, 3, $-OCH_3$).

Anal. Calcd for $C_{15}H_7N_3O_9$: C, 48.27; H, 1.89; N, 11.26; O, 38.58. Found: C, 48.27; N, 1.83; N, 11.26; O, 38.73.

4,5,7-Trinitro-9-dicyanomethylenefluorene-2-carboxylic Acid (VIII).—To a refluxing mixture of 7.0 g (1.7×10^{-2} mol) of 4,5,7-trinitrofluorenone-2-carboxylic acid and 200 ml of dry methanol, 2.2 g (3.4×10^{-2} mol) of malononitrile and 3 drops of piperidine were added. After 24 hr, the solution was cooled to room temperature and filtered to afford 4.7 g (60%) of orange 4,5,7-trinitro-9-dicyanomethylenefluorene-2-carboxylic acid, mp 307–310°.

Anal. Calcd for $C_{17}H_5N_5O_8$: C, 50.14; H, 1.24; N, 17.19; O, 31.43. Found: C, 49.98; H, 1.58; N, 16.93; O, 31.51.

4,5,7-Trinitro-9-dicyanomethylenefluorene-2-carboxylic Acid Chloride (VIIIb).—A mixture of 1.0 g (2.4×10^{-3} mol) of 4,5,7-trinitro-9-dicyanomethylenefluorene-2-carboxylic acid and 25 ml of thionyl chloride was refluxed for 18 hr. The excess thionyl chloride was removed under reduced pressure and the residue was recrystallized from toluene to give 0.2 g (20%) of a solid melting at 292–300°.

Anal. Calcd for $C_{17}H_4ClN_5O_7$: C, 47.97; H, 0.95; Cl, 8.33; N, 16.45; O, 26.31. Found: C, 50.50; H, 1.47; Cl, 6.46; N, 16.40; O, 25.25.

Even though the analysis isn't too good, it is noted that at least 80% of the theroetical amount of chlorine is present. The high carbon and hydrogen values, as well as the other low values, can be explained on the basis of tightly complexed toluene in the final product.

Methyl 4,5,7-Trinitro-9-dicyanomethylenefluorene-2-carboxylate (VIIIc).—To a mixture of methyl 4,5,7-trinitrofluorenone-2-carboxylate (1.0 g; 2.7×10^{-3} mol) and 75 ml of methanol at reflux, 0.4 g (3×10^{-3} mol) of malononitrile and 1 drop of piperidine were added. After 4 hr, the solution was concentrated to 0.5 the volume and cooled overnight in the cold room. Filtration afforded 0.85 g (66%) of methyl 4,5,7-trinitro-9-dicyanomethylenefluorene-2-carboxylate melting at 269–273°.

Anal. Calcd for $C_{18}H_7N_5O_8$: C, 51.32; H, 1.68; N, 16.62; O, 30.38. Found: C, 51.04; H, 1.78; N, 16.54; O, 30.48.

2,5,7-Trinitrofluorenone-4-carboxylic Acid (XX).—By a procedure analogous to the preparation of 4,5,7-trinitrofluorenone-2-carboxylic acid, there was obtained 8.5 g (59%) of 2,5,7-trinitrofluorenone-4-carboxylic acid from fluorenone-4-carboxylic acid. The compound melted at 256–61°.

Anal. Calcd for $C_{14}H_5N_3O_9$: C, 46.81; H, 1.40; N, 11.70; O, 40.08. Found: C, 46.03; H, 1.90; N, 11.31; O, 40.80.

Methyl 2,5,7-Trinitrofluorenone-4-carboxylate (XXI).—This compound was prepared in the same way as methyl 4,5,7-trinitrofluorenone-2-carboxylate from 2,5,7-trinitrofluorenone-4-carboxylic acid. It melted at 183–184° and was obtained in 22% yield (0.9 g).

Anal. Calcd for $C_{15}H_7N_3O_9$: C, 48.27; H, 1.89; N, 11.26; O, 38.58. Found: C, 48.31; H, 2.20; N, 11.16; O, 38.58.

2,5,7-Trinitro-9-dicyanomethylenefluorene-4-carboxylic Acid (IXa).—To a refluxing mixture of 4.5 g (1.1×10^{-2} mol) of 2,5,7-trinitrofluorenone-4-carboxylic acid and 200 ml of methanol, 1.5 g (2.2×10^{-2} mol) of malononitrile and 3 drops of piperidine were added. After refluxing for 24 hr, the solution was cooled in an ice bath and the orange solid collected. The 2.0 g (40%) of 2,5,7-trinitro-9-dicyanomethylenefluorene-4-carboxylic acid melted at 313–5°.

Anal. Calcd for $C_{17}H_5N_5O_8$: C, 50.14; H, 1.24; N, 17.19; O, 31.43. Found: C, 50.02; H, 1.84; N, 17.09; O, 31.20.

2,5,7-Trinitro-9-dicyanomethylenefluorene-4-carboxylic Acid Chloride (IXb).—A mixture of 1.0 g (2.4×10^{-2} mol) of 2,5,7-trinitro-9-dicyanomethylenefluorene-4-carboxylic acid and 25 ml of thionyl chloride was refluxed for 18 hr. The excess thionyl chloride was removed under reduced pressure and the residue recrystallized from toluene to give a low yield (<10%) of a solid melting at 293–294°.

Anal. Calcd for $C_{17}H_4ClN_5O_7$: C, 49.97; H, 0.95; Cl, 8.33; N, 16.45; O, 26.31. Found: C, 48.50; H, 1.26; Cl, 7.84; N, 16.47; O, 25.32.

Methyl 2,5,7-Trinitro-9-dicyanomethylenefluorene-4-carboxylate (IXc).—Malononitrile (0.2 g, 3×10^{-3} mol) and 1 drop of piperidine were added to a refluxing mixture of 0.5 g (1.3×10^{-3} mol) of methyl 2,5,7-trinitrofluorene-4-carboxylate and 50 ml of dry methanol. After 4 hr, the mixture was concentrated to 0.5 the volume and cooled overnight in the cold room. Filtration gave 0.40 g (57%) of methyl 2,5,7-trinitro-9-dicyanomethylenefluorene-4-carboxylate melting at 285–7°.

Anal. Calcd for $C_{18}N_7N_5O_8$: C, 51.32; H, 1.68; N, 16.62; O, 30.38. Found: C, 51.25; H, 1.80; N, 16.22; O, 30.73.

Phenyliminodiethanol Dibenzoate (XXIV).—A mixture of 9.1 g (5×10^{-2} mol) of phenyliminodiethanol (Matheson Coleman and Bell), 15.5 g (0.12 mol) of benzoyl chloride and 50 ml of pyridine was heated to 50° for 3 hr. The reaction mixture was poured onto ice water; the solid was collected and recrystallized from 400 ml of methanol to give 17.2 g (88%) of phenyliminodiethanol dibenzoate, mp 71.5° (lit.[13] 77°).

Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.59; O, 16.43. Found: C, 74.06; H, 6.09; N, 3.62; O, 16.18.

***p*-Anisyliminodiethanol Dibenzoate (XXV).**—A mixture of *p*-anisyliminodiethanol (10.6 g, 5×10^{-2} mol), benzoyl chloride (15.5 g; 0.12 mol) and 50 ml of pyridine gave *p*-anisyliminodiethanol dibenzoate by the same procedure used for XVII. One crystallization gave 10.6 g (50%) of XVIII, mp 62.4°.

Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34; O, 19.07. Found: C, 70.87; H, 6.04; N, 3.38; O, 19.65.

Charge-Transfer Complexes. Materials.—The aromatic hydrocarbons (Table II) were used as received from the Aldrich Chemical Company. The syntheses of the aromatic monoamines are described above while the preparation of the phenyliminodiethanol polymers was previously described.[3b] TMPD was obtained from Matheson Coleman and Bell (MCB), converted to the dihydrochloride, recrystallized from 2-propanol, neutralized with sodium hydroxide and finally sublimed. It melted at 50°.[12]

The synthesis of the fluorene acceptors (Vc–IXc) are described above. Chloranil was obtained from MCB and recrystallized from benzene, mp 287°. DDQ was obtained from Aldrich Chemical Company and recrystallized from chloroform, mp 201°.

Spectra.—All measurements were made with a Cary 14 spectrophotometer using 1,1,2,2-tetrachloroethane of Spectrograde quality as solvent.

(13) B. C. Mc Kusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and H. F. Mower, *J. Amer. Chem. Soc.* **80**, 2806 (1958).

Registry No.—Va, 24867-37-6; Vc, 24929-23-5; VIa, 24867-38-7; VIc, 24867-39-8; VIIa, 24867-40-1; VIIb, 24867-41-2; VIIc, 24867-42-3; VIIIa, 24867-43-4; VIIIb, 24867-44-5; VIIIc, 24867-45-6; IXa, 24867-46-7; IXb, 24867-47-8; IXc, 24867-48-9; XIV, 24929-24-6; XVII, 24929-25-7; XVIII, 24867-49-0; XX, 24929-26-8; XXI, 24867-50-3; XXIV, 24867-51-4; XXV, 24867-52-5.

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Equilibrium in the Addition of Hydrogen Peroxide, Water, and Methanol to Acetone[1a]

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Equilibrium constants of 5.3×10^{-2}, 2.5×10^{-5}, and 1.9×10^{-4} M^{-1} have been determined for the addition of hydrogen peroxide, water, and methanol to acetone. These equilibrium constants and values from the literature for hydroxylamine, hydrogen cyanide, and bisulfite ions give a satisfactory linear logarithmic plot against the γ of Sander and Jencks.

In connection with a study of the basicity of various nucleophilic reagents toward carbon,[2] equilibrium constants for the addition of hydrogen peroxide, water, and methanol to acetone were needed. These constants were determined by proton magnetic resonance (pmr) measurements.

Results

The addition of hydrogen peroxide to aqueous solutions of acetone gave rise to a new pmr peak at about τ 8.64 in addition to the acetone peak at about 7.84 ppm. The area of this new peak relative to that of the acetone peak grew over a period of hours, especially at high concentrations of hydrogen peroxide and acetone. This growth was more rapid when the solutions were made 0.001 M in perchloric acid but became unobservable in the presence of 0.1 M sodium acetate. By analogy to the fact that hemiacetal formation is both acid and base catalyzed and is fairly rapid in neutral solutions, whereas acetal formation is only acid catalyzed, we assumed that equilibrium in the addition of hydrogen peroxide to acetone had already been established by the time (about 1 hr) the first pmr measurements were made. The subsequent, slower, acid-catalyzed reaction is thought to consist of the formation of 2,2-bis(hydroperoxy)propane, as shown in eq 2. In addition,

$$Me_2CO + H_2O_2 \rightleftharpoons Me_2C(OH)OOH \quad (1)$$

$$Me_2CO + 2H_2O_2 \rightleftharpoons Me_2C(OOH)_2 \quad (2)$$

various other peroxide derivatives of acetone[3] were probably being formed to at least some extent. This interpretation of our results is consistent with the chemical shifts to be expected for the monohydroperoxy and bishydroperoxy products shown in eq 1 and 2. The new peak absorbs 0.80 ppm upfield from acetone. The methyl peaks for paraldehyde and acetaldehyde diethyl acetal appear 0.80 and 0.88 ppm, respectively, upfield from the methyl peak of acetaldehyde.[4] Since a hydroperoxy group has essentially the same effect as a hydroxy group on the chemical shift of a β proton,[5] the mono- and bishydroperoxy compounds would be expected to have about the same chemical shift. That this is the case is further supported by the observation to be described later in this paper that the pmr peaks

(1) (a) This investigation was supported in part by Grant GP-7629 from the National Science Foundation. (b) The Ohio State University. (c) NSF Undergraduate Research Participant, summer, 1964.

(2) J. Hine and R. D. Weimar, Jr. *J. Amer. Chem. Soc.*, **87**, 3387 (1965).

(3) *Cf.* N. A. Milas and A. Golubović, *ibid.*, **81**, 6461 (1959), and references listed therein.

(4) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, No. 6, 143; N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "High Resolution NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, no. 474.

(5) W. D. Wilk, A. L. Allred, B. A. Koven, and J. A. Marshall, *J. Chem. Soc. B*, 565 (1969).

for the hydrate and the methyl hemiacetal of acetone are 0.78 ppm upfield from that for acetone. It is therefore not surprising that the formation of the bishydroperoxide is not accompanied by the formation of a new pmr peak but merely by the growth (with some broadening, however) of the peak attributed to the monohydroperoxide. If reaction 1 is the only process that is occurring to a significant extent, its equilibrium constant (K) may be calculated from eq 3, where $[H_2O_2]_0$

$$K = \frac{1 - f}{f([H_2O_2]_0 - f[Me_2CO]_0)} \qquad (3)$$

and $[Me_2CO]_0$ are the concentrations of hydrogen peroxide and acetone originally added, and f is equal to the area of the peak at about τ 8.65 divided by the sum of the areas of the peaks at 8.65 and 7.85 ppm. Values of K calculated from measurements on solutions 0.1 M in sodium acetate are listed in Table I. No clear trends

TABLE I

EQUILIBRIUM IN THE ADDITION OF HYDROGEN PEROXIDE TO ACETONE IN AQUEOUS SOLUTION AT 35°[a]

$[Me_2CO]_0$, M	$[H_2O_2]_0$, M	K, M^{-1}	K', N^{-1}
2.74	1.89	0.061	0.028
5.48	1.89	0.044	0.020
4.11	2.52	0.069	0.030
5.48	2.52	0.070	0.030
2.74	3.15	0.047	0.022
5.48	3.15	0.042	0.020
		Av 0.056 ± 0.011	0.025 ± 0.004

[a] Solutions contained 0.1 M sodium acetate to prevent reaction 2. Each equilibrium constant is the average of two to four measurements.

accompany changes in concentrations of acetone and hydrogen peroxide, perhaps because of the fairly large experimental uncertainty in the values of K.

The conditions that sufficed to establish equilibrium in reaction 1 might also bring about equilibrium in the addition of the hydroperoxy group of the product of reaction 1 to another molecule of acetone as shown in eq 4. We have no convincing evidence as to whether

$$Me_2C(OH)OOH + Me_2CO \rightleftharpoons Me_2C(OH)OOC(OH)Me_2 \qquad (4)$$

reaction 4 is taking place or not, but its probable effect on our determination of K may be estimated as follows. Let us assume that the oxygen-bound hydroxy group in $Me_2C(OH)OOH$ has the same tendency to add to acetone that such a group in hydrogen peroxide does, neglecting statistical effects.[6] Then we may define an equilibrium constant for the addition of oxygen-bound hydroxy groups to acetone as shown in eq 5. In eq 5,

$$K' = \frac{[Me_2C(OH)OO-]}{[Me_2CO][-OOH]} \qquad (5)$$

$[-OOH]$ is the concentration, in equivalents per liter of oxygen-bound hydroxy groups, and $[Me_2C(OH)OO-]$ is that of peroxy-complexed acetone. In terms of the symbols used in eq 3, K' may be calculated as shown in eq 6. Values of K' are also given in Table I. If the

$$K' = \frac{1 - f}{f(2[H_2O_2]_0 - f[Me_2CO]_0)} \qquad (6)$$

(6) In view of the possibility of steric effects, this assumption seems to give a reasonable maximum for the probable importance of reaction 4.

assumptions on which the calculation of K' was based are correct, then K must equal $2K'$ since K refers to hydrogen peroxide, which has two peroxy OH groups that can add. Thus the assumption that K' is a constant leads to the value 0.050 M^{-1} for K, a value only 10% smaller than the one calculated with the complete neglect of reaction 4.

The values of K calculated from data on solutions containing no sodium acetate usually increased with time, and after 24 hr, values as large as 0.5 M^{-1} were obtained.

When the pmr spectra of aqueous solutions containing about 20% acetone by volume were run at high amplitude on a 60-MHz instrument, a peak was noted about 47 Hz (0.78 ppm) upfield from the principal acetone peak. This peak was considerably smaller than the ^{13}C satellite peaks, 65 Hz on either side of the acetone peak. There was no matching peak 0.78 ppm downfield from acetone, and the peak was also observed in the pmr spectrum of 20% solutions of acetone in deuterium oxide. For the reasons described in discussing the hydrogen peroxide adducts of acetone, this chemical shift is plausible for acetone hydrate (2,2-propanediol). We therefore utilized the fact that the spectrum of an aldehyde hydrate may be fused with that of the corresponding aldehyde in aqueous solution by the addition of acid to speed the hydration–dehydration reactions.[7] In the presence of 0.0001 M perchloric acid the acetone hydrate peak could no longer be detected.

To be sure that the difference between the acetone peak and the peak we were attributing to the hydrate was a chemical shift rather than some sort of coupling, the pmr spectra of 20% solutions of acetone in protium oxide and deuterium oxide were run on a 100-MHz spectrometer. The new peak was now found on the other side of the upfield ^{13}C satellite of acetone, 78 Hz (0.78 ppm) upfield from acetone.

In order to determine the equilibrium constant for hydration, the area of the peak due to acetone hydrate was compared with that of the nearby ^{13}C satellite, whose area was assumed to be 0.55% that of the acetone peak. (The natural abundance of ^{13}C is 1.1%.) Measurements on the 60-MHz spectra of 20% solutions gave 0.15 ± 0.07% as the extent of hydration of the acetone, but measurements at 100 MHz gave 0.11 ± 0.03% in protium oxide and 0.09 in one set of measurements in deuterium oxide solution. The values at 100 MHz are based on larger and more reproducible peaks and are therefore believed to be more reliable. The equilibrium constant for hydration in 80% protium oxide corresponds to 0.14 ± 0.04% hydration in 100% protium oxide.

The pmr spectrum of a 28 vol % solution of acetone in methanol was found to contain a peak 0.78 ppm upfield from acetone. For reasons of the type described in consideration of addition of water and hydrogen peroxide to acetone, this peak was attributed to the hemiacetal. Its area was 0.59 ± 0.07 that of the nearby ^{13}C satellite of acetone, and therefore the equilibrium constant for the addition of methanol to acetone is (19 ± 2) × 10^{-5} M^{-1}. When about 1.2 vol % of acetone was dissolved in methanol and ultraviolet measurements were made quickly at 25°, the absorbance at 2700 Å was found to decrease rapidly (half-life about 15 sec).

(7) Cf. J. Hine and J. G. Houston, J. Org. Chem., **30**, 1328 (1965).

Extrapolation of measured absorbance values to zero time gave 0.44 ± 0.10% as the extent of the decrease, corresponding to an equilibrium constant of (18 ± 4) × 10^{-5} M^{-1}.

Discussion

The equilibrium constants for addition to acetone obtained in this study are listed in Table II; also listed

TABLE II
EQUILIBRIUM CONSTANTS FOR ADDITION TO ACETONE[a]

Addend	K, M^{-1}	γ[b]
H_2O[c]	2.5×10^{-5}	−3.58
MeOH[d]	1.9×10^{-4}	−2.22
H_2O_2[e]	5.3×10^{-2}	−0.64
H_2NOH[f,g]	1.0	1.24
HCN[h]	14	2.44
HSO_3^-[i]	1.5×10^{2}	4.02

[a] In aqueous solution at 35° unless otherwise noted. [b] From ref 8. [c] At 33°. [d] In methanol. [e] An average of the two equally plausible values, 0.056 and 0.050 M^{-1}, is listed. [f] W. P. Jencks, *J. Amer. Chem. Soc.*, 81, 475 (1959). [g] At 25°. [h] D. P. Evans and J. R. Young, *J. Chem. Soc.*, 1310 (1954). [i] Extrapolated from data of ref 9 at 0, 20, and 30°.

are values determined by other investigators. Sander and Jencks have measured equilibrium constants for a number of additions to aldehydes and have suggested the parameter γ as a measure of the ability of a reagent to add to a carbonyl group.[8] Numerical values of γ were obtained from the defining equation

$$\gamma_{HX} = \log \frac{K_{HX}}{K_{MeNH_2}}$$

where K_{HX} and K_{MeNH_2} are equilibrium constants for the addition of the reagent in question and methylamine to pyridine-4-carboxaldehyde in water at 25°. In Figure 1 is a plot of the values of log K from Table II *vs.* γ. The K value for addition of hydrogen peroxide was divided by a statistical factor of two in accord with the practice of Sander and Jencks. The points give fairly good agreement with the least-squares line shown. The slope of this line (0.93) would be 0.96 for data at 25° if all the entropies of addition were identical. The actual deviation of the points from a straight line may be smaller than that shown. The point for bisulfite, which is low, was taken from the data of Gubareva,[9] whose equilibrium constant for benzaldehyde is stated by Sousa and Margerum[10] to be too low (by a factor of more than fivefold) because of dissociation of the adduct during titration of the bisulfite ions. Since the bisulfite addition compound of acetone dissociates about half as fast as the one derived from benzaldehyde,[11] the reported K for acetone[9] may also be too low, but probably by a smaller factor than that found for benzaldehyde.[10] The point for hydroxylamine is too high, but this is the only point not determined at 35 ± 2° and it would probably be lower at that temperature.

The equilibrium constant we have observed for the addition of methanol to acetone is smaller by a factor of about 800 than the value reported in dioxane at 26 ± 1°.[12] However, the measurements in dioxane were made by the method of Wheeler,[13] in which an acid catalyst was used, and Kubler and coworkers have shown that under the conditions used, the disappearance of aldehyde or ketone is due largely to the formation of an acetal rather than a hemiacetal.[14,15] Therefore, we think that our value for methanol is more reliable. The fact that the point for methanol falls somewhat below the line in Figure 1 may be due to a solvent effect or to steric hindrance. We believe that the number of compounds studied is not enough to show whether there are certain categories of reagents that give deviations from a plot of log K *vs.* γ, as was found to be the case for formaldehyde.[8]

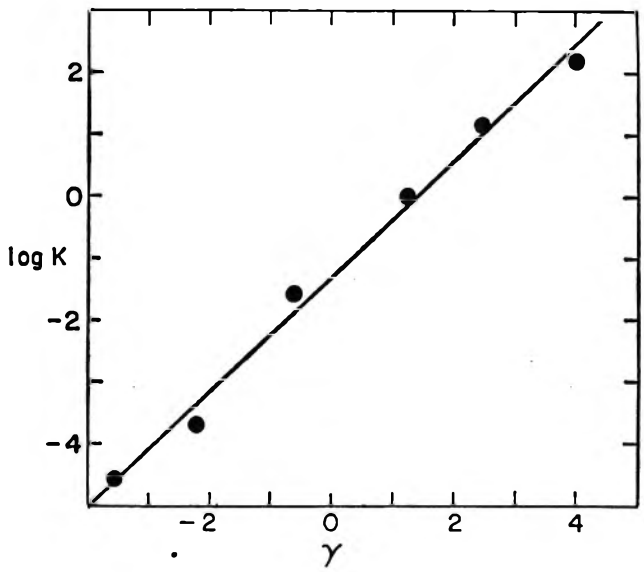

Figure 1.—Log-log plot of equilibrium constants for addition to acetone at 35° *vs.* those for addition to pyridine-4-carboxaldehyde at 25°.

Experimental Section[16]

Addition of Hydrogen Peroxide.—Reagent acetone and "30%" hydrogen peroxide solutions were used, the strength of the latter being determined by refractive index measurements and by permanganate titration with satisfactory agreement. Pmr peak areas were measured by electronic integration. Each of the equilibrium constants in Table I is the result of two to four measurements made at various times between 1 and 48 hr after the solutions were mixed; no tendency of the equilibrium constant to drift was noted.

Ultraviolet measurements at about 2700 Å on about 1 M aqueous solutions of acetone and hydrogen peroxide using cells with 1-mm path lengths showed that the absorbance was smaller than that which would be expected from the amounts of acetone and hydrogen peroxide that had been added. This difference between observed and "expected" absorbance was larger in solutions 0.001 M in perchloric acid than in solutions 0.001 M in sodium bicarbonate. The fact that the absorbance of the hydrogen peroxide solutions was comparable with that of acetone solutions of about the same strength complicated the quantitative.

(8) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).
(9) M. A. Gubareva, *Zh. Obshch. Khim.*, **17**, 2259 (1947); *Chem. Abstr.*, **42**, 4320c (1948).
(10) J. D. Sousa and J. D. Margerum, *J. Amer. Chem. Soc.*, **82**, 3013 (1960).
(11) D. A. Blackadder and C. Hinshelwood, *J. Chem. Soc.*, 2720 (1958).
(12) J. M. Jones and M. L. Bender, *J. Amer. Chem. Soc.*, **82**, 6322 (1960)
(13) O. H. Wheeler, *ibid.*, **79**, 4191 (1957).
(14) D. G. Kubler and L. E. Sweeney, *J. Org. Chem.*, **25**, 1437 (1960).
(15) J. M. Bell, D. G. Kubler, P. Sartwell, and R. G. Zepp, *ibid.*, **30**, 4284 (1965).
(16) Pmr spectra were run using Varian spectrometers, a Model A-60 with a probe temperature of 35 ± 1° and a Model HA-100 with a probe temperature of about 33°. Chemical shifts are given relative to external TMS, and their absolute values are therefore not very reliable. Ultraviolet measurements were made using a Cary spectrophotometer, Model 14 at 25 ± 1°.

interpretation of the uv data, however, and this possible method for measuring the equilibrium constant was abandoned.

Hydration of Acetone.—The pmr spectra of 20 and 30 vol % solutions of acetone in water were determined at 60 MHz. At high amplitude a peak was observed 0.78 ppm upfield from acetone. This peak, whose size was not much larger than that of the background noise in the case of the noisier spectra, was shown, by changing the spin rate, not to be a spinning side-band. Its area and that of the nearby ^{13}C satellite of acetone were determined by counting squares. The spectra at 100 Hz were run 9–10 times and the results were averaged using a computer of average transients; then the whole process was repeated. Two other spectra were run using very slow sweep, very small response, and very large spectrum amplitude.

Addition of Methanol.—Pmr measurements at 60 MHz on solutions of acetone in methanol were made in a manner analogous to that used for the aqueous solutions. In a typical uv measurement, 0.035 ml of acetone was added to 3.0 ml of methanol and absorbance measurements were made as quickly as possible at 2760 Å using an equilibrated ketone solution with an absorbance of 1.467 in the reference cell. The observed absorbance decreased from 0.808 at 16 sec to an equilibrium value of 0.803. Extrapolation to zero time gave a value of 0.813. This change of 0.010 in a total absorbance of 2.280 corresponds to 0.44%. When small amounts of hydrochloric acid were added, much larger decreases in absorbance were observed.

Registry No.—Hydrogen peroxide, 7722-84-1; water 7732-18-5; methanol, 67-56-1; acetone, 67-64-1.

Acknowledgment.—We are indebted to Mr. Steven H. Williams for making the pmr measurements at 100 MHz, to Dr. Donald G. Kubler for valuable discussions of our results, and to the National Science Foundation for grants that aided in the purchase of the nmr spectrometers and the ultraviolet-visible spectrophotometer, whose purchase was also made possible by a generous grant from the Charles F. Kettering Foundation.

Effects of Fluorine Substitution upon Glycidyl Ether–Dibutylamine Reaction Rates

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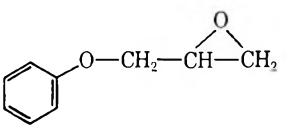
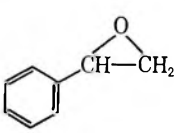
Two series of fluorine-substituted glycidyl ethers have been synthesized, and their rates of reaction with dibutylamine in *t*-amyl alcohol have been measured by means of gas chromatography. The reaction was found to be second order, with dibutylamine attacking the terminal position of the epoxide ring in all cases. Fluorinated substituents generally decreased the reaction rates within each series with one outstanding exception. Rate constants and Arrhenius parameters are presented for each of the reactions studied.

1,2-Epoxy-3-phenoxypropane (1a), or phenyl glycidyl ether,[1] is three to four times more reactive toward nucleophilic attack by amines in alcohol than either styrene oxide (2) or allylbenzene oxide (3).[2] It has



1a



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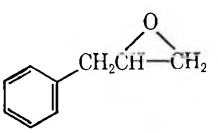

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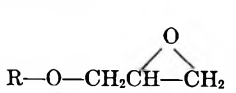
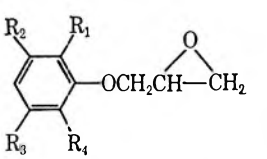
been suggested[3,4] that this increased reactivity is characteristic of all epoxides of the glycidyl ether type represented by structure 4.



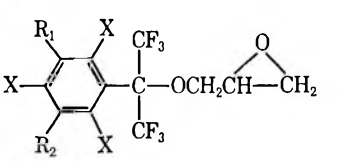
4

In order to determine the effects responsible for the reactivity of this type of compound, it is of interest to measure the influence of variations in the R group of 4 upon the epoxide–amine reaction rate. Although previous workers have studied the effects of solvents and the use of various nucleophiles on the rate of cleavage of the epoxide ring,[5,6] in each investigation only a single glycidyl ether was used. A comparison of the reaction rates of different glycidyl ethers under identical conditions has not to our knowledge been made.

We have prepared two series of fluorine-containing glycidyl ethers, of general structure 1 and 5, in order to



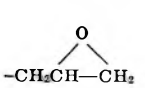
1a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_3 = R_4 = H$; $R_2 = CF_3$
c, $R_1 = R_2 = R_3 = R_4 = F$



5a, $R_1 = R_2 = H$; $X = H$
b, $R_1 = CF_3$; $R_2 = H$; $X = H$
c, $R_1 = R_2 = CF_3$; $X = H$
d, $R_1 = R_2 = F$; $X = F$

determine the effect of increasing fluorine substitution upon the rates of ring opening of these epoxides. Compounds of type 5 represent a new class of fluoro-substituted glycidyl ethers. The present paper describes the preparation of these compounds, and presents kinetic data comparing the rates of epoxide–dibutylamine reaction, in *t*-amyl alcohol, for the glycidyl ethers above.

(1) The term "glycidyl" is used to denote the following structure.



(2) N. B. Chapman, N. S. Isaacs, and R. E. Parker, *J. Chem. Soc.*, 1925 (1959).

(3) S. O. Greenlee, "Thioxyalkanoic Acids and Epoxy Curing Agents," paper presented to the American Chemical Society Division of Organic Coatings & Plastics Section, Minneaplis, Minn., April 1969.

(4) W. J. Patterson and N. Bilow, *J. Polym. Sci., Part A*, **7**, 1089 (1969).

(5) L. Shechter, J. Wynstra, and R. P. Turkjy, *Ind. Eng. Chem.*, **48**, 94 (1956).

(6) Shechter and J. Wynstra, *ibid.*, **48**, 86 (1956).

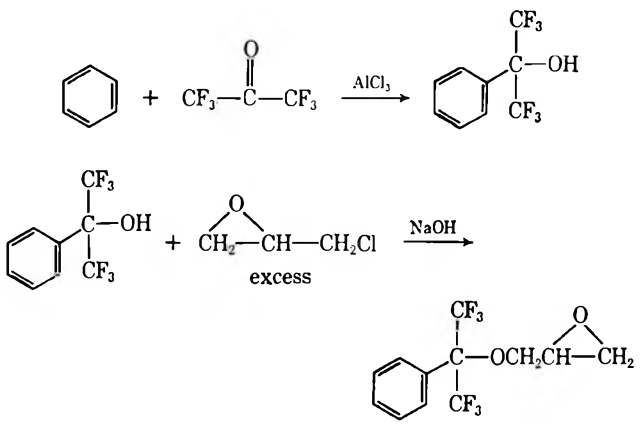
TABLE I

PHYSICAL DATA FOR FLUORO-SUBSTITUTED GLYCIDYL ETHERS[a,b]

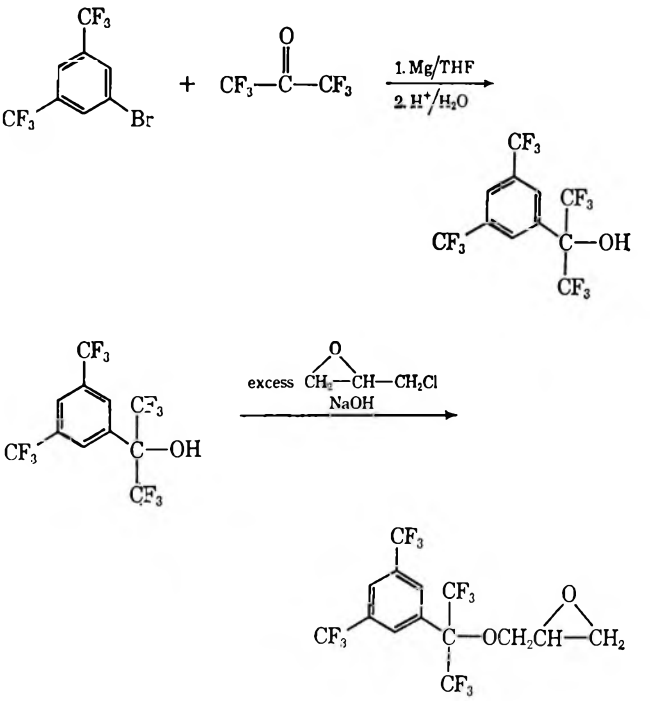
Compd	Yield, %[c]	Bp, °C (10.0 mm)	$n^{20}D$	Nmr spectrum[d,e] (R–O–CH_2–CH–CH_2) $H_{aromatic}$	H_a	H_b	H_c
1b	88	110	1.4676	7.10 (4)	4.16	3.18	2.76
					3.89		2.60
1c	67	99	1.4552	6.79 (1)	4.41	3.26	2.77
					4.09		2.59
5a	65	104	1.4371	7.56 (2)	3.82	3.15	2.75
				7.46 (3)	3.57		2.60
5b	78	108	1.4095	7.92 (1)	3.91	3.20	2.78
				7.68 (3)	3.57		2.63
5c	62	97	1.3901	8.16 (2)	3.99	3.25	2.84
				8.03 (1)	3.53		2.67
5d	38	111	1.4074		3.63	3.18	2.78
							2.51

[a] Satisfactory analytical data were obtained for all compounds in this table. [b] Epoxy equivalent weights were determined, using 1 *N* pyridine hydrochloride in pyridine, for all compounds except **5d**, and are within 1.5% of the theoretical value. [c] Per cent conversion from corresponding hydroxy compound. [d] Ppm downfield from tetramethylsilane in CCl_4 solution. [e] Listing of dual signals for H_a or H_c indicates chemical nonequivalence of the geminal protons.

SCHEME I



SCHEME II



Discussion and Results

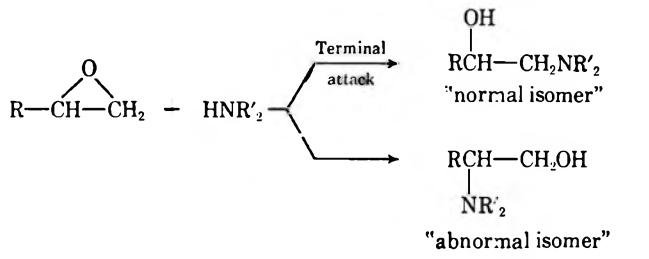
Synthesis of Glycidyl Ethers.—We have found that aryl bis(trifluoromethyl)carbinols react with excess epichlorohydrin in much the same manner as do phenols.[7] This reaction is a convenient new means for obtaining 2,3-epoxy-1-propoxy compounds, or glycidyl ethers, which contain fluorocarbon. The acidic carbinol intermediates may be obtained *via* direct, $AlCl_3$-catalyzed condensation of aromatic hydrocarbons with hexafluoroacetone[8] (Scheme I), or by means of aromatic Grignard reagents (Scheme II). We have found fluoroalkyl-substituted aromatics to be unreactive toward hexafluoroacetone in the presence of $AlCl_3$, presumably owing to ring deactivation by electronegative substituents. Therefore, the alternate synthesis *via* the Grignard reagent was employed for compounds **5b–d**.

Table I contains physical properties and yields for the four new glycidyl ethers of type **5** prepared by this method. Also included are compounds **1b** and **1c**, which were prepared from the corresponding phenols and epichlorohydrin by the method of Kelly, *et al.*[7]

(7) P. B. Kelly, A. J. Landau, and C. D. Marshall, *J. Appl. Polym. Sci.*, **6**, 431 (1962).

(8) B. S. Farah, E. E. Gilbert, and J. P. Sibilia, *J. Org. Chem.*, **30**, 998 (1965).

Nature of the Reaction.—The reaction between a secondary amine and an unsymmetrical epoxide compound may proceed *via* two different pathways, depending upon which of the epoxide-ring carbons is attacked.



Terminal attack, leading to the formation of a secondary alcohol, is the exclusive or predominant pathway

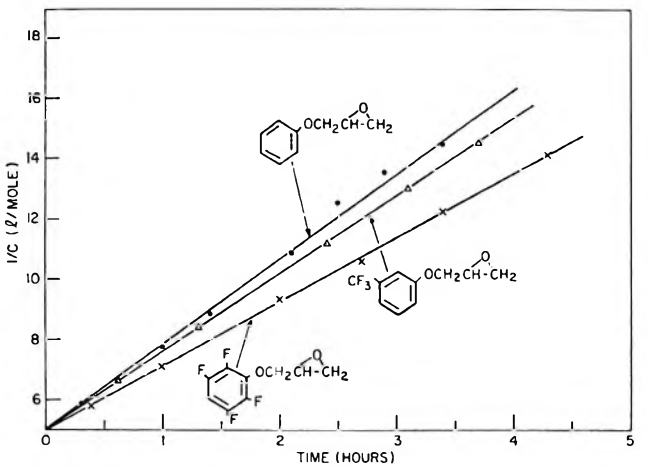


Figure 1.—Reaction of dibutylamine with glycidyl ethers of type 1 in *t*-amyl alcohol (T = 60°), using equimolar amounts of reactants. Reciprocal concentration of the glycidyl ether is plotted as a function of time.

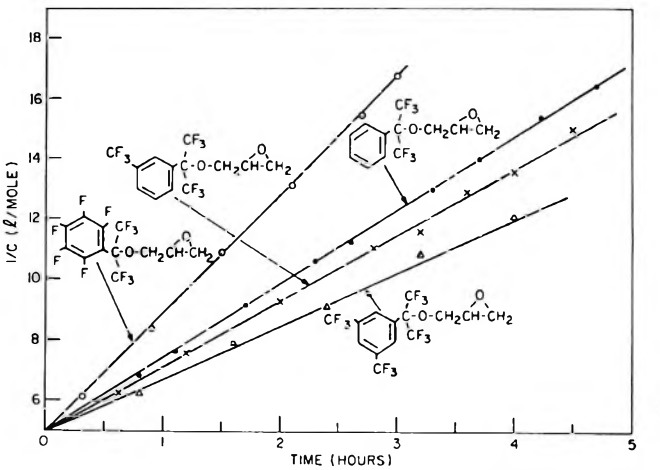


Figure 2.—Reaction of dibutylamine with glycidyl ethers of type 5 in *t*-amyl alcohol (T = 60°), using equimolar amounts of reactants. Reciprocal concentration of the glycidyl ether is plotted as a function of time.

followed by nearly all nucleophiles under neutral or basic conditions.[9-11] This is due primarily to the steric hindrance exerted by the R group on the more substituted ring carbon atom. The product corresponding to terminal attack is commonly labeled the "normal isomer," because of the overwhelming tendency for this mode of reaction. Previous workers[2] have shown that phenyl glycidyl ether and piperidine conform to the trend, reacting in ethanol to give greater than 99% normal isomer.

Our kinetic data were obtained by treating various glycidyl ethers with dibutylamine, using *t*-amyl alcohol as a solvent. Because dibutylamine is even more hindered than is piperidine, a negligible yield of abnormal isomers is expected under the reaction conditions employed. Investigation of the products of each of the glycidyl ether–dibutylamine reactions supported this prediction. Glpc analysis of the reaction mixtures at various column temperatures indicated only a single, sharp product peak in each case. These products were identified by their nmr spectra as the corresponding normal isomers (see Experimental Section). No evidence of formation of the abnormal isomer could be detected, using these techniques, for any of the systems. For this reason, and in light of the above discussion, we have considered terminal attack to be the exclusive reaction pathway for the kinetic studies reported. The formation of trace amounts of abnormal isomer, although not rigorously excluded, would have a negligible effect on our rate measurements.

The possibility of alcoholysis of the epoxide ring by solvent molecules has been ruled out by previous studies. It has been shown[2] that ethanol does not attack phenyl glycidyl ether in neutral solution, and even refluxing in the presence of phenoxide anion led to only 2% reaction between ethanol and phenyl glycidyl ether.[11] Our work was carried out using hindered *t*-amyl alcohol at 60° or less; so it is not surprising that no sign of alcoholysis was found.

Order of the Reaction.—As anticipated by various studies, which show that nucleophilic attack on an epoxide ring in neutral or basic media proceeds according to second-order kinetics,[12,13] all of the glycidyl ethers, **1a-c** and **5a-d**, follow a second-order rate law in their reactions with dibutylamine. Using equal initial concentrations of amine and glycidyl ether in *t*-amyl alcohol, and plotting the reciprocal of the glycidyl ether concentration as a function of time, we obtained good straight lines for each system at three different reaction temperatures (Figures 1 and 2). This linear behavior is characteristic of second-order reactions. Concentrations were determined as a function of time by analyzing aliquots of the reaction solution in the gas chromatograph, and measuring integrated peak areas as percentages of initial areas. This technique allows for determination of the amounts of each reactant remaining at any time. However, rate measurements were based only upon the glycidyl ether concentrations, which could be determined more accurately owing to complete isolation of the gas chromatographic peak. It was clear from the simultaneous measurement of the amine concentration that a 1:1 reaction was taking place.

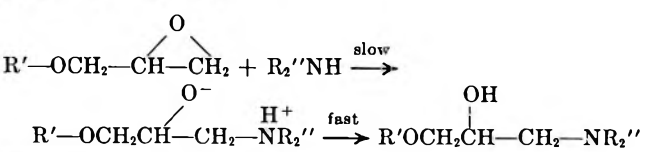
$$\frac{dC_A}{dt} = -k_2 C_A C_B$$

$$\text{for } C_A = C_B$$

$$\frac{dC_A}{dt} = -k_2 C_A^2$$

$$\frac{1}{C_A} = -k_2 t + C_A^0$$

Predicted Effect of Fluorinated Substituents.—Because of the second-order appearance of these reactions, it seems clear that the mechanism is SN2, with dibutylamine attacking the terminal carbon of the epoxy ring in the rate-determining step. This slow step may then be followed by rapid proton transfer, probably *via* the hydroxylic solvent.[5]



(9) E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 106–114.

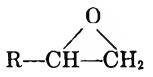
(10) S. Winstein and R. B. Henderson, *Heterocycl. Compounds*, **1**, 22 (1950).

(11) G. L. Brode and J. Wynstra, *J. Polym. Sci., Part A*, **4**, 1045 (1966).

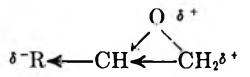
(12) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(13) N. S. Isaacs and R. E. Parker, *J. Chem. Soc.*, 3497 (1959).

It has been inferred[2] from this mechanism that the sharp increase in reactivity of phenyl glycidyl ether (**1a**) compared with styrene oxide (**2**) or 1,2-epoxy-3 phenylpropane (**3**) in ethanol is due to polarization of the bonds in structure **6a** as in **6b**. The overall effect of



6a



6b

polarizing the epoxy ring in this fashion is to facilitate the reaction by enhancing the approach of the nucleophilic amine.[2,14] It was felt that the greater electronegativity of phenoxymethyl *vs.* phenyl or benzyl activated the epoxide ring, thereby causing its increased reactivity. If we extend this reasoning to the introduction of fluorine into the aromatic nucleus of **1a**, the subsequent increase in electronegativity of that part of the molecule is expected to produce an epoxide even more reactive than **1a** itself. Tetrafluorophenoxy, for example, being more electron withdrawing than phenoxy, should cause tetrafluorophenyl glycidyl ether (**1c**) to react with nucleophiles faster than does phenyl glycidyl ether (**1a**). This argument also pertains to compounds of type **5**, in which increased fluorine substitution on the aromatic nucleus should coincide with increasing rate constants.

Observed Effect of Fluorinated Substituents.—For both series of analogous compounds the surprising finding of our kinetic studies is that increased fluorine substitution on the aromatic ring slows the rate of epoxide ring opening in all cases but one. The actual decrease in reactivity is substantial, in view of the fact that the substituents are quite distant from the site of attack.

As seen in Figures 1 and 2, and in Table II, rate constants tend to decrease rather than increase as fluorinated substituents are added to **1a** and **5a**. Only compound **5d** exhibits the predicted acceleration in its reaction with dibutylamine. For all other compounds, there is a decrease in reactivity within each series which is roughly proportional to the degree of fluorine substitution. Arrhenius parameters for the reactions studied are given in Table III. As can be seen, activation energies and entropies are quite similar in all cases.

TABLE II

MEASURED RATE CONSTANTS

Compd	$10^4 k_2$[a] (T = 41°)	$10^4 k_2$ (T = 51°)	$10^4 k_2$ (T = 60°)
1a	2.96	5.28	8.15
1b	2.72	4.87	7.59
1c	2.41	3.83	6.00
5a	2.68	4.88	7.03
5b	2.24	3.81	6.17
5c	1.78	3.27	5.12
5d	4.78	7.71	11.14

[a] k_2 in l. mol^{-1} sec^{-1}.

TABLE III

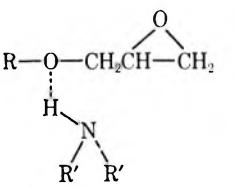
ARRHENIUS PARAMETERS

Compd	E_a, kcal/mol	Log A	$\Delta S^{\ddagger}$,[a] eu
1a	11.0 ± 1	4.2 ± 0.5	−42 ± 3
1b	11.2 ± 1	4.3 ± 0.5	−41 ± 3
1c	10.4 ± 1	3.6 ± 0.5	−44 ± 3
5a	10.5 ± 1	3.7 ± 0.5	−44 ± 3
5b	10.9 ± 0.6	3.9 ± 0.3	−43 ± 2
5c	11.4 ± 1	4.2 ± 0.5	−42 ± 3
5d	9.3 ± 1	3.2 ± 0.5	−46 ± 3

[a] Activation parameter, calculated at 300°K according to J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley New York, N. Y., 1963, p 71.

Mechanistic Considerations.—The steric situation in the vicinity of the epoxide ring is identical for each of the compounds of type **1**, as it is for those of type **5**. Therefore, differences in reactivity within the two groups of compounds must be attributed to electronic effects caused by substituents on the aromatic ring, or to steric considerations involving the glycidyl ether oxygen, rather than the epoxide ring itself.

The unexpected behavior of fluorine-substituted compounds led us to consider an alternative to the simple inductive explanation for the highly reactive nature of glycidyl ethers in the SN2 reactions discussed. The assumption of activation of the epoxide ring *via* a simple inductive effect is inconsistent with the observed deactivating influence of fluorinated substituents in compounds **1a–c** and **5a–c**. Therefore, we suggest that at least part of the activation caused by the glycidyl ether oxygen may be due to its ability to hydrogen bond with the attacking amine as in **7**.[15]



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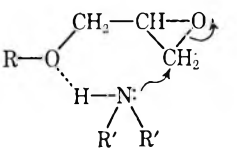

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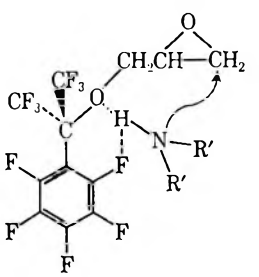
Association of this type between the amino hydrogen and the ether oxygen would enhance the approach of the amine, and place it in a favorable position for attacking the epoxide ring. In the six-membered-ring intermediate (**8**) which results from terminal attack the ether oxygen might also stabilize the transition state by delocalizing the positive charge on the nitrogen during formation of the C–N bond. This mechanism is consistent with the absence of the abnormal isomer, which would require a five- rather than six-membered-ring intermediate for its formation. Fluorine or fluorocarbon substituents on the R group of **8** are expected to decrease the electron density around the glycidyl ether oxygen, and consequently reduce its ability to associate with the amino hydrogen. Formation of a complex such as **8** should, therefore, be less favored. If this effect outweighs the activation of the epoxide ring due to polarization (as in **6b**), it would account for the decreasing rate constants corresponding to increasing fluorine content in compounds **1a–c** and **5a–c**.

Compound **5d**, our most heavily fluorinated epoxide, is anomalous to the trend of deactivation by fluorine substitution, and in fact is the most reactive of all the glycidyl ethers studied. Only this compound, of the seven tested, reacts faster than phenyl glycidyl ether. It seems unlikely that the inductive effect of the fluo-

(14) C. N. Hinshelwood, K. J. Laidler, and E. W. Timm, *J. Chem. Soc.*, 848 (1938).

(15) It has been suggested that the reactions of epoxy resins of the glycidyl ether type with amine curing agents are accelerated by this mechanism. [A. L. Cupples, H. Lee, and D. G. Stoffey, *Advan. Chem. Ser.*, **92**, 173 (1970)].

rine in this case should suddenly activate the epoxide ring, since the trend established in all other cases is toward deactivation. A study of the molecular model of compound **5d** suggests one possible explanation for its anomalous behavior. Owing to the steric hindrance of the two *ortho* fluorine atoms, the *gem*-trifluoromethyl groups in this molecule appear to be somewhat constrained perpendicular to the aromatic ring. The preferred orientation appears to be that shown, in which the glycidyl ether oxygen is found to be very close to one of the *ortho* fluorine atoms. It appears that a



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complex such as **8** could be formed not only through association of the amino hydrogen with the glycidyl ether oxygen, but also with the *ortho* fluorine atoms as in **9**. Of the compounds studied, then, **5d** seems to be unique for two reasons: (1) the rotation of the *gem*-trifluoromethyl groups may be hindered by adjacent fluorine substituents, and (2) fluorine atoms (on the benzene ring) are positioned such that association with the amino hydrogen might lead to a favorable geometry for attack on the epoxide ring. One or both of these factors may be responsible for the anomalous behavior of this compound. Synthesis of compounds closely related to **5d** is in progress, in order to determine the basic requirements for enhanced reactivity in fluoro-substituted glycidyl ethers.

Experimental Section

Nuclear magnetic resonance spectra were obtained at 24° as 10–20% solutions in CCl_4 on a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were run as smears of the neat liquids between salt plates on a Perkin-Elmer Model 457 grating spectrophotometer. All glycidyl ethers were fractionated on a Nester–Faust auto annular Teflon spinning-band still (10.0 mm) prior to use in kinetic experiments. Analytical samples of the glycidyl ethers were used for all kinetic runs. Elemental analyses were performed at the Schwarzkopf Laboratories, N. Y.

Materials.—Phenyl glycidyl ether was purchased from the Shell Chemical Company, and purified by distillation through the column described above. Starting materials including 2,3,5,6-tetrafluorophenol, 3-trifluoromethylphenol, 3-bromobenzotrifluoride, 3,5-di(trifluoromethyl)bromobenzene, hexafluoroacetone, and pentafluorophenyl bromide were obtained from Peninsular ChemResearch Co., and used as received. 2-Phenyl-2-hydroxyhexafluoropropane was prepared from benzene and hexafluoroacetone according to published procedure.[8]

The dibutylamine used for kinetic studies was purified by careful distillation through a 3-ft, helices-packed column. A single fraction, bp 158–159° (760 mm), was used for all runs. Distillation of the *t*-amyl alcohol was carried out on the same column, and the central fractions, bp 101.0–101.5° (760 mm), were combined for use. After purification, neither the amine nor the alcohol solvent showed any traces of impurity in the gas chromatograph. All runs were made using materials from the same batch of amine, and from the same batch of solvent, to ensure further against variations in the relative reaction rates due to trace impurities. The glycidyl ethers used showed no traces of impurity by glpc analysis on the columns described below.

2-(3-Trifluoromethylphenyl)hexafluoro-2-propanol.—3-Bromobenzotrifluoride, 41 g (0.18 mol), magnesium turnings, 4.5 g (0.19 g-atom), precleaned with dilute hydrochloric acid and dried, and 100 ml of anhydrous ether were placed into a 100-ml, four-necked resin kettle equipped with a magnetic stirrer, gas inlet tube and a Dry Ice–acetone reflux condenser protected from the atmosphere by a drying tube. Prior to reactant addition, the kettle was heated with a heat lamp and purged with dry nitrogen. When the flask contents were gently heated, the reaction started and proceeded smoothly for 0.5 hr to yield a dark brown solution. Hexafluoroacetone, 22 ml (0.19 mol), was condensed into a trap from a cylinder, and then allowed to distil over into the resin kettle above the liquid surface at such a rate to maintain gentle reflux at the Dry Ice condenser. The addition required 1.5 hr during which the Grignard solution was stirred vigorously. Excess 2 *N* hydrochloric acid was used to decompose the magnesium salt after the reactant solution had stirred overnight. Additional ether was added, and the ethereal solution was separated, washed twice with water and once with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was fractionated through a 6-in., vacuum-jacketed Vigreux column. The fraction boiling at 89° (44 mm) was collected as a clear, colorless liquid, 36 g (63% overall yield based on starting bromide). The product was alkali soluble, and the nmr spectrum in carbon tetrachloride displayed signals at δ 8.02 (s, 1, Ar–H), 7.70 (m, 3, Ar–H), and 3.40 (s, 1, O–H). The infrared spectrum had a sharp hydroxyl peak at 3600 cm^{-1} and a broad one between 3500 and 3200 cm^{-1}.

2-[3,5-Di(trifluoromethyl)phenyl]hexafluoro-2-propanol.—This compound was prepared *via* the Grignard reaction in essentially the same manner as the preceding intermediate, except that a mixture of ether and tetrahydrofuran was required as solvent. Magnesium could not easily be induced to react with 3,5-di(trifluoromethyl)bromobenzene in dry ether alone. A 60-g (0.205 mol) sample of the bromide gave an overall yield of 54.3 g (70%) of the desired product: bp 85–90° (40 mm); nmr δ 8.20 (s, 2, Ar–H), 8.03 (s, 1, Ar–H), 3.79 (s, 1, O–H). The infrared spectrum contained a sharp hydroxyl peak at 3610 cm^{-1}.

2-(Pentafluorophenyl)hexafluoro-2-propanol.—This perfluorinated alcohol was synthesized *via* the readily produced Grignard reagent of pentafluorophenyl bromide in dry ether. In this case, the reaction between the Grignard reagent and hexafluoroacetone appeared to be unusually sluggish, and it was necessary to heat the ethereal solution nearly to boiling in order to achieve a moderately rapid reaction. From 50 g (0.20 mol) of bromide was obtained 45 g (64% overall yield) of the alcohol, bp 167–170° (760 mm). The infrared spectrum had a sharp hydroxyl band at 3620 cm^{-1}.

Preparation of Glycidyl Ethers.—All of the glycidyl ethers were prepared in essentially the same manner. The procedure for preparation of the glycidyl ether of 2-(3-trifluoromethylphenyl)-hexafluoro-2-propanol (**5b**) is typical.

Into a 2-l., three-necked, round-bottom flask equipped with a reflux condenser, dropping funnel and stirrer were placed 195 g (0.65 mol) of 2-(3-trifluoromethylphenyl)hexafluoro-2-propanol, 500 g epichlorohydrin (5.4 mol), 600 ml acetone and 70 ml water. Into the dropping funnel was placed a 20% aqueous solution of sodium hydroxide containing 28.0 g (0.70 mol) of the alkali. The flask contents were stirred and heated to reflux. One-sixth of the sodium hydroxide solution was added slowly, and reflux was continued 15 min before another one-sixth portion was added. This was repeated until five-sixths of the alkali had been added, and, after the fifth reflux period, the aqueous layer was drawn off and discarded. Then, reflux was resumed and the remaining alkali solution was added. After 15 min, the aqueous layer was again withdrawn. Most of the acetone and epichlorohydrin was distilled at atmospheric pressure, and the remaining solution was decanted from a residual precipitate of sodium chloride. The solution was then diluted with 300 ml of ether. This ethereal solution was washed once with water and twice with saturated aqueous sodium chloride. After it was dried over anhydrous sodium sulfate, the solution was filtered, and the ether was removed on a rotary evaporator. The resulting product solution was vacuum distilled through a 6-in. Vigreux column and a fraction boiling at 120° (13 mm) was collected; 180 g (78%) of 2-(3-trifluoromethylphenyl)hexafluoro-2-propyl glycidyl ether were obtained. This was redistilled through the Nester–

Faust spinning-band column to yield 151 g of analytically pure product (Table I).

Rate Measurements.—Gas chromatographic analyses were performed using a Beckman GC-2A gas chromatograph, equipped with a 10-in. recorder and Disc integrator, and containing a 2 ft × 0.25 in. column of 30% silicone 550 on 42–60 mesh firebrick. Concentrations were obtained as a function of time by comparing the integrated area of a reactant peak at time t with the area of that peak at time t_0. Since the t_0 peak corresponded to a known initial concentration, the actual concentration at time t was found from the ratio of peak areas.

In a typical run, 2.00×10^{-4} mol of glycidyl ether and 2.00×10^{-4} mol of dibutylamine were weighed into a 10-ml volumetric flask, and enough *t*-amyl alcohol was added to bring the total volume to exactly 10 ml.[16,17] The solution was then immediately transferred to a round-bottom flask equipped with a magnetic stirrer and a self-sealing rubber septum cap. The flask was capped and placed in a constant temperature bath, which was maintained at the reaction temperature ±0.05°. The t_0 reading was then taken by piercing the septum cap with a syringe and withdrawing a 10.0-μl aliquot, which was injected directly into the gas chromatograph for analysis. Subsequent 10.0-μl samples were withdrawn at various times and analyzed in an identical manner. Variation in the height of the sharp *t*-amyl alcohol peak, which served as an internal standard, was generally less than 1% during a run, and never more than 2.5%. All reactions were followed to at least 60% completion.

Each of the reactions was run at three different temperatures (41.0, 51.0, and 60.0°) using initial concentrations of 0.200 *M* in *t*-amyl alcohol for each reactant. All of the 60° reactions were run in duplicate. Rate constants were reproducible to within 1% in most cases, and to within 3% in the least favorable case.

Product Analysis.—Product investigation was done by glpc analysis of the infinite-time kinetic samples. A 6 ft × 0.25 in. column packed with 30% Ucon 50 HB 2000 on 42–60 mesh firebrick was used for analytical and preparative work.

Glpc analysis of the reaction mixtures indicated a single, sharp product peak for each of the reactions. After purification by preparative glpc, these products were characterized by their nmr spectra as the "normal" isomers (products of terminal attack by the amine on the epoxide ring). No trace of the second (abnormal) isomer could be found in any of the systems. In each case, the ratio of the nmr integral of the N-C-H *vs.* O-C-H protons was 2:1, corresponding to that required for the normal isomer.

Since all products are identical on the amino side of the glycidyl ether oxygen, the features of interest in their spectra are extremely similar. These features are illustrated by the following example.

Adduct of Dibutylamine and Glycidyl Ether 1c.—The reaction product had a retention time of 2.5 min at 35 psig, T = 200°, on the column described above. Its nmr spectrum showed maxima at δ 6.73 (triplet of triplets, 1, Ar-H), 4.18 (d, 2, O-CH_2) 3.83 (m, 1, CHOH), 3.60 (s, 1, O-H), 2.52 (m, 6, N-CH_2), 1.36 (m, 8, C-CH_2), 0.93 (t, 6, CH_3).

The infrared spectrum showed absorptions at 3440 cm^{-1} (hydroxyl); 2900, 1460 (C-H): 1640, 1540, and 1490 (aromatic); 1175 (Ar-O-R); and 1100 (C-F, alcoholic C-O).

Registry No.—**1a**, 122-60-1; **1b**, 585-45-5; **1c**, 25056-10-4; **5a**, 25056-11-5; **5b**, 25056-12-6; **5c**, 25056-13-7; **5d**, 25080-58-4; 2-(3-trifluoromethylphenyl)-hexafluoro-2-propanol, 25056-14-8; 2-[3,5-di(trifluoromethyl)phenyl]hexafluoro-2-propanol, 25056-15-9; 2-(pentafluorophenyl)hexafluoro-2-propanol, 13732-52-0; adduct of dibutylamine and glycidyl ether **1c**, 25056-17-1.

Acknowledgment.—We wish to thank Mr. C. F. Poranski and Dr. W. B. Moniz for running the nmr spectra.

(16) In an unpublished study involving neat solutions of dibutylamine and the glycidyl ethers above, we have shown that the error introduced by allowing the reactants to be in contact during weighing is about 0.1%. This slight error has been ignored in our measurements.

(17) Initial concentrations were corrected for the expansion of the solution upon heating from room temperature to reaction temperature.

Ozonation of Amines. IV.[1] Di-*t*-butylamine

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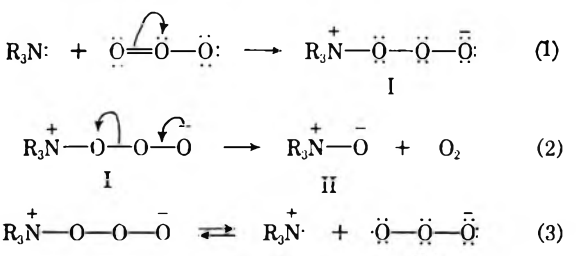
Results of a thorough study of the ozonation of a secondary amine, di-*t*-butylamine, are reported for the first time. The major final products from ozonation in chloroform are 2-methyl-2-nitropropane, di-*t*-butylammonium chloride, and various derivatives of the *t*-butyl group lost in formation of the nitro compound. In contrast to the ozonation of *t*-butylamine, the ozonate anion radical is not produced initially, but di-*t*-butyl nitroxide is. To explain these results a new (fourth) fate of the amine–ozone adduct is proposed.

The first paper of this series[2] initiated a systematic study of the ozonation of primary, secondary, and tertiary aliphatic amines in which the alkyl groups are varied as to whether they are primary, secondary, or tertiary. A working hypothesis was presented in the preceding papers[1-3] as a rationale for the reactions found both by us and others to occur during the ozonation of amines. This involved the formation of an initial amine–ozone adduct (I, eq 1) followed by three fates thereof: (a) loss of molecular oxygen with formation of an amine oxide (II, eq 2) or further reaction products thereof; (b) an intramolecular side-chain oxidation; (c) homolytic dissociation to a nitrogen cation radical (III) and the ozonate anion radical (IV, eq 3), followed by reactions of these. Paper II[3] reported the results of ozonation of tri-*n*-butylamine, a tertiary amine with primary alkyl groups, for which the major competitive fates of the amine–ozone adduct (I) were amine oxide formation (eq 2) and side-chain oxidation. Paper III[1] discussed the ozonation of *t*-butylamine, a primary amine having a tertiary alkyl group, for which the major fates of I were those of eq 2 and 3.



(1) Part III: P. S. Bailey and J. E. Keller, *J. Org. Chem.*, **33**, 2680 (1968).

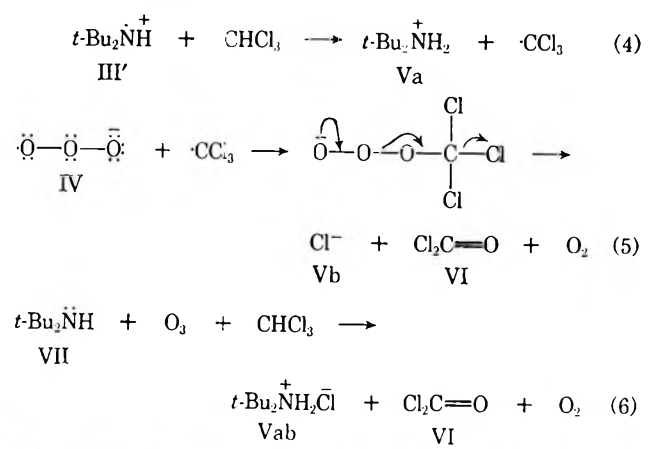
(2) P. S. Bailey, J. E. Keller, D. A. Mitchard, and H. M. White in "Oxidation of Organic Compounds. III," Advances in Chemistry Series, No. 77, American Chemical Society, Washington, D. C., 1968, pp 58–64.

(3) P. S. Bailey, D. A. Mitchard, and A. Y. Khashab, *J. Org. Chem.*, **33**, 2675 (1968).

The present paper deals with the first detailed study of the ozonation of a secondary amine, di-*t*-butylamine (VII), although one particular aspect of the ozonation of several aromatic and alicyclic secondary amines has previously been reported.[4a] In addition, the present paper presents a low-temperature epr study of the ozonation of both *t*-butylamine and di-*t*-butylamine.

The ozonations of di-*t*-butylamine were carried out in chloroform at −60 to −65°, methylene chloride at −75°, and carbon tetrachloride at −20°, usually with nitrogen as a carrier. Typical experiments are shown in Table I. As was true also in the case of *t*-butylamine,[1] the experiments in chloroform are easier to interpret and will be discussed first.[4b] The ratio of ozone (with nitrogen carrier, expt 1–3) to amine reacting was approximately equal to 2, regardless of whether excess ozone was employed or whether that used was insufficient to react with all of the starting amine. Likewise the yields of products were approximately the same in either case. This indicates that any intermediate products reacted almost as quickly as they were formed. The major products were 2-methyl-2-nitropropane (X), di-*t*-butylammonium chloride (Vab), *t*-butyl alcohol (XI), acetone, and molecular oxygen. In addition, traces of di-*t*-butyl peroxide, *t*-butyl chloride, isobutylene, and di-*t*-butyl nitroxide (VIII) were found. The sum of the yields of *t*-butyl alcohol, acetone, di-*t*-butyl peroxide, *t*-butyl chloride, and isobutylene was equal to 85–90% of the 2-methyl-2-nitropropane yield, thus accounting for most of the *t*-butyl group lost in the formation of the nitro compound. For each millimole of ozone which reacted during the ozonation, approximately 0.7 mmol of molecular oxygen was evolved.

The reactions involved in the ozonation of di-*t*-butylamine (VII) are obviously more complex than those occuring during the ozonation of *t*-butylamine.[1]



(4) (a) S. D. Razumovskii, A. L. Buchachenko, A. B. Shapiro, E. G. Rozantsev, and G. E. Zaikov, *Proc. Acad. Sci. USSR, Chem. Sect.*, **183**, 1086 (1968). (b) A possible question concerns the reaction of ozone with chloroform in the absence of added substrate. In our earlier paper[1] we showed that ozone reacts with chloroform much more slowly than with *t*-butylamine under comparable conditions and that essentially no hydrogen chloride is produced by the reaction. Experience has shown that solvents reactive toward ozone may be used in ozonations without themselves reacting appreciably, provided the substance being ozonized is more reactive than the solvent; see P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958). For example, methanol is an excellent ozonolysis solvent, even though alone it is very reactive toward ozone. In the ozonation of *t*-butylamine[1] chloroform was used as an effective trap for the nitrogen cation radical, just as methanol is used as a trap for the Criegee zwitterion. In the present work with di-*t*-butylamine, the ammonium chloride product is not ascribed to reaction of ozone with chloroform, since it also was obtained in similar yield from ozonation in carbon tetrachloride. The latter does not react appreciably with ozone.

Since, however, a major product from ozonation of both amines in chloroform was the corresponding ammonium chloride, one would initially assume that the mechanisms leading to the salt were the same in each case. For di-*t*-butylamine (VII), by analogy to *t*-butylamine,[1] this would involve eq 1–5, the summation of which produces eq 6. The odor of phosgene (VI) was strong in the reaction mixture, and it was shown independently that, whereas *t*-butylamine and phosgene react to give *t*-butyl isocyanate and/or N,N′-di-*t*-butylurea[1], no urea was produced when di-*t*-butylamine and phosgene were mixed.

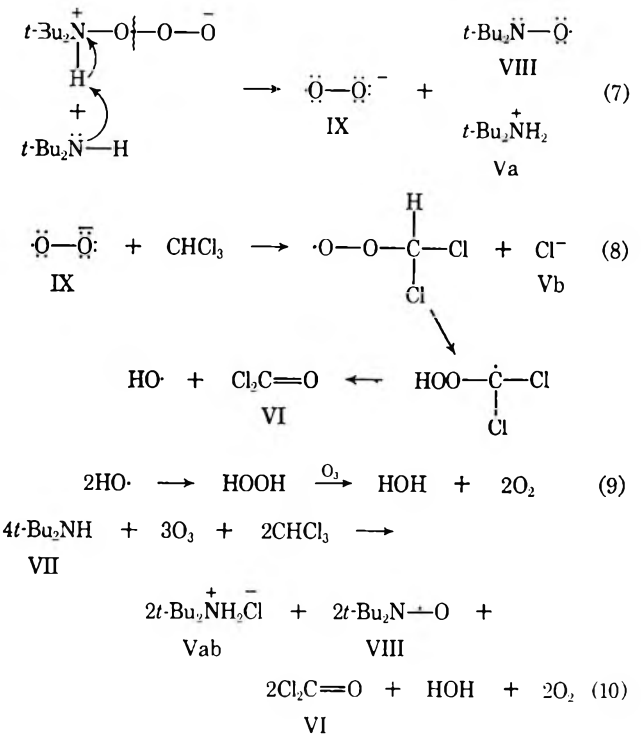
The assumption that the mechanisms leading to salt formation were the same for the ozonations of *t*-butylamine[1] and di-*t*-butylamine was shown to be invalid by low-temperature epr studies. Ozonation of *t*-butylamine in pentane at −120° gave immediately a red solution. An epr spectrum of the solution gave a strong signal for the ozonate anion radical (IV) in the form of a singlet with a *g* value of 2.0107.[5] Further ozonation produced a red precipitate which, by analogy to the ozonation of ammonia,[5] must have been *t*-butylammonium ozonate. The singlet for the ozonate anion radical was also observed during ozonation of *t*-butylamine in methylene chloride at −90°. It decayed rapidly, however. Thus, the nitrogen cation radical–ozonate anion radical (eq 3) route to *t*-butylammonium chloride during ozonation of *t*-butylamine in chlorinated solvents[1] was confirmed. In contrast, however, epr spectra taken during the ozonation of di-*t*-butylamine in pentane at −120°, in Freon 11 (dichlorodifluoromethane) at −115°, and in methylene chloride at −90° showed no signal whatsoever for the ozonate anion radical (IV). Instead, the characteristic triplet for di-*t*-butyl nitroxide[6,7] (VIII) immediately and strongly appeared. In order to make certain that the signal for the ozonate anion radical (IV) could be observed if present, a mixture of *t*-butylamine and di-*t*-butylamine was ozonized in pentane at −120°, and the reaction was monitored by epr spectroscopy. Signals for both the ozonate anion radical and di-*t*-butyl nitroxide were strongly present. This clearly shows that the amine–ozone adduct fate depicted by eq 3 does not occur to any detectable extent with di-*t*-butylamine. It also strongly suggests that di-*t*-butyl nitroxide (VIII) is a primary product of the ozonation of di-*t*-butylamine (VII). Evidence for the intermediacy of nitroxide radicals in the ozonation of secondary amines has also been reported by Razumovskii, *et al.*[4a] Working with certain aromatic and alicyclic amines, they reported high yields of the nitroxides in some cases.

In order to account for these facts, a fourth fate of the amine–ozone adduct (I) is proposed. This is illustrated by eq 7 followed by eq 8 and 9. If these are combined with eq 1, an overall equation is obtained (eq 10) which describes the ozonation of di-*t*-butylamine in chloroform to the corresponding ammonium salt and di-*t*-butyl nitroxide, etc.

(5) I. J. Solomon, K. Hattori, A. J. Kacmarek, G. M. Platz, and M. J. Klein, *J. Amer. Chem. Soc.*, **84**, 34 (1962), report a *g* value of 2.0119.

(6) A. K. Hoffmann, A. M. Feldman, E. Gelblum, and W. G. Hodgson, *ibid.*, **86**, 639 (1964).

(7) Superimposed on the nitroxide triplet was also a less intense triplet with a splitting constant equal to that reported for the 2-methyl-2-nitropropane anion radical; see A. K. Hoffman, W. G. Hodgson, D. L. Maricle, and W. H. Jura, *ibid.*, **86**, 631 (1964).



The reactions of eq 7 provide a route both to the ammonium cation (Va) and to di-*t*-butyl nitroxide (VIII) as an initial product. The driving force would be the formation of the stable nitroxide *via* a transition state which involves both the amine–ozone adduct and a second amine molecule. The oxygen anion radical (IX) is well known and readily formed.[8] Its attack on the solvent is a logical route to the chloride anion (Vb) moiety of di-*t*-butylammonium chloride (Vab), as shown in eq 8. The fact that the yield of ammonium salt was very little less with carbon tetrachloride solvent (expt 6) than with chloroform and about the same as with methylene chloride (expt 5) is in agreement with this mechanism. This was not true with *t*-butylamine, where the route to salt, after the formation of the ion radicals (eq 3), was more complicated in carbon tetrachloride than in chloroform or methylene chloride.[1]

The oxygen anion radical (IX) could also be the cause of the formation of trace amounts of the 2-methyl-2-nitropropane anion radical,[7] through release of an electron to a nitroalkane (X) molecule which had been produced from ozonation of di-*t*-butyl nitroxide (VIII), as described below. Epr spectra taken during the ozonation of di-*t*-butyl nitroxide alone (in absence of di-*t*-butylamine) show no signal for the nitroalkane anion radical.

In the accompanying paper[9] the results of ozonation of di-*t*-butyl nitroxide (VIII) are discussed. Equation 11 portrays reasonably well the stoichiometry of the reaction. The fact that the products are essentially the same as those obtained from ozonation of di-*t*-butylamine provides added evidence for the intermediacy of di-*t*-butyl nitroxide (VIII) in the ozonation of di-*t*-butylamine (VII).

Equation 12 is a combination of eq 10 and 11. It does not portray exactly the stoichiometry of the ozonation of di-*t*-butylamine, since Table I shows that 2-

(8) D. L. Maricle and W. G. Hodgson, *Anal. Chem.*, **37**, 1562 (1965).
(9) P. S. Bailey and J. E. Keller, *J. Org. Chem.*, **35**, 2782 (1970).

TABLE I
OZONATIONS OF DI-*t*-BUTYLAMINE

Expt	Solvent,[a] m	Amine, mmol: Starting	Reacting[b]	O_3,[c] mmol: Passed	Reacted	O_3/amine[d]	O_2 evolved, mmol	*t*-BuNO: yield, mmol	%	*t*-$Bu_2NH_2Cl^-$: yield, mmol	%	*t*-BuOH: yield, mmol	%	MeC(=O)O: yield, mmol	%	Other products, yield,[e] mmol	%	% N[f]	% *t*-Bu[g]
1	$CHCl_3$, 15	2.36	2.36	6.5	4.9	2.1	3.4	1.29	55	0.98	42	0.64	27	0.47	20	0.02[h]	1	96	90
2	$CHCl_3$, 15	2.32	2.32	6.4	5.2	2.2	*i*	1.26	54	1.01	44	0.65	28	0.40	17	0.03[h]	1	98	90
3	$CHCl_3$, 15	5.00	3.10	6.0	6.0	1.9	4.2	1.74	56	1.32	43	0.73	23	0.54	17	*i*		99	83
4	$CHCl_3$, 25	2.33	2.33	5.5[j]	4.3	1.8	*i*	1.60	69	0.74	32	1.00	43	0.30	13	0.03[k]	1	100	89
5	CH_2Cl_2, 25	2.33	2.33	7.5	6.5[j]	2.8[j]	*i*	1.61	69	0.77	33	0.89	38	0.43	18	0.01[m]		100	91
6	CCl_4, 8	1.13	1.13	Excess			*i*	*i*			36	*i*		*i*		*i*		*i*	*i*
	8	1.04	1.04	5.0	3.6		*i*				33								

[a] The ozonations in $CHCl_3$ solvent were carried out at −60 to −65°, the one in CH_2Cl_2 at −75°, and those in CCl_4 at −20°. [b] The millimoles of amine reacting is equal to the millimoles of starting amine minus the millimeters of amine detected at the end of the experiment. [c] All ozonations except no. 4 were with ozone–nitrogen. [d] Ratio of ozone reacting to amine reacting. [e] All percentage yields are based on the amount of amine reacting. [f] Per cent accounting of *nitrogen* in products from amine reacting. [g] Per cent accounting in products of the second *t*-butyl group (which is lost in production of the nitro compound). [h] Di-*t*-butyl peroxide (0.01 mmol), *t*-butyl chloride (0.01 mmol), isobutylene (trace to 0.01 mmol). [i] Not determined. [j] Oxygen rather than nitrogen was the ozone carrier. [k] *t*-Butyl chloride (0.03 mmol), the rest undetermined. [l] Value could be slightly high. [m] Isobutylene (0.014 mmol), the rest undetermined.

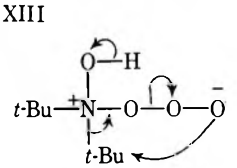
methyl-2-nitropropane (X) is always produced in larger amounts than di-*t*-butylammonium chloride (Vab). There must be some other, relatively minor, reaction occurring which yields 2-methyl-2-nitropropane during ozonation of di-*t*-butylamine (VII) without going through di-*t*-butyl nitroxide (VIII) as an intermediate. We suggest that this involves the amine oxide fate of the initial amine–ozone adduct (eq 2). Rearrangement of the amine oxide (XII) of di-*t*-butylamine to di-*t*-butylhydroxylamine (XIII, eq 13) followed by ozonation of XIII can logically give the nitro compound (X) plus *t*-butyl hydroperoxide (XIV), eq 14). Ozonation of *t*-butyl hydroperoxide is known to give *t*-butyl alcohol as the major product (eq 15), although small amounts of acetone, di-*t*-butyl peroxide, and *t*-butyl chloride are also obtained.[10] Combination of eq 1, 2, 13, 14, and 15 gives eq 16 as a representation of the overall reaction involving di-*t*-butylhydroxylamine as an intermediate. This combined with eq 12 gives eq 17, which in most details depicts accurately the stoichiometry of the ozonation of di-*t*-butylamine, especially the ratios of salt, nitroalkane, *t*-butyl alcohol, and acetone.

$$\underset{\text{VIII}}{4t\text{-Bu}_2\dot{\text{N}}\text{—O}} + 8\text{O}_3 + 2\text{CHCl}_3 \longrightarrow \underset{\text{X}}{4t\text{-BuNO}_2} + \underset{\text{XI}}{2t\text{-BuOH}} + 2(\text{CH}_3)_2\text{C}{=}\text{O} + \text{Cl}_2 + 2\text{Cl}_2\text{C}{=}\text{O} + \text{CH}_3\text{OH} + \text{H}_2\text{C}{=}\text{O} + 6\text{O}_2 \quad (11)$$

$$8t\text{-Bu}_2\text{NH} + 14\text{O}_3 + 6\text{CHCl}_3 \longrightarrow 4t\text{-Bu}_2\overset{+}{\text{N}}\text{H}_2\overset{-}{\text{Cl}} + 4t\text{-BuNO}_2 + 2t\text{-BuOH} + 2(\text{CH}_3)_2\text{C}{=}\text{O} + 6\text{Cl}_2\text{C}{=}\text{O} + \text{Cl}_2 + \text{CH}_3\text{OH} + \text{H}_2\text{C}{=}\text{O} + 2\text{H}_2\text{O} + 10\text{O}_2 \quad (12)$$

$$\underset{\text{XII}}{t\text{-Bu}_2\overset{+}{\text{N}}(\text{H})\text{—}\overset{-}{\text{O}}} \longrightarrow \underset{\text{XIII}}{t\text{-Bu}_2\ddot{\text{N}}\text{OH}} \quad (13)$$

$$\underset{\text{XIII}}{t\text{-Bu}_2\ddot{\text{N}}\text{OH}} + \text{O}_3 \longrightarrow$$



$$\longrightarrow \underset{\text{X}}{t\text{-BuNO}_2} + \underset{\text{XIV}}{t\text{-BuOOH}} \quad (14)$$

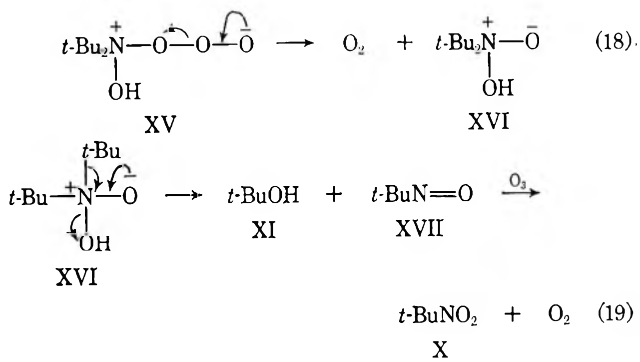
$$\underset{\text{XIV}}{t\text{-BuOOH}} + \text{O}_3 \longrightarrow \underset{\text{XI}}{t\text{-BuOH}} + 2\text{O}_2 \quad (15)$$

$$\underset{\text{VII}}{t\text{-Bu}_2\text{NH}} + 3\text{O}_3 \longrightarrow \underset{\text{X}}{t\text{-BuNO}_2} + \underset{\text{XI}}{t\text{-BuOH}} + 3\text{O}_2 \quad (16)$$

$$9t\text{-Bu}_2\text{NH} + 17\text{O}_3 + 6\text{CHCl}_3 \longrightarrow 4t\text{-Bu}_2\overset{+}{\text{N}}\text{H}_2\overset{-}{\text{Cl}} + 5t\text{-BuNO}_2 + 3t\text{-BuOH} + 2(\text{CH}_3)_2\text{C}{=}\text{O} + 6\text{Cl}_2\text{C}{=}\text{O} + \text{Cl}_2 + \text{CH}_3\text{OH} + \text{H}_2\text{C}{=}\text{O} + 2\text{HOH} + 13\text{O}_2 \quad (17)$$

One discrepancy in eq 17, however, is that the ratio of ozone reacting to amine reacting is too low (*cf.* expt 1–2, Table I). This could result from the fact that the equation does not take into account the reactions of ozone with methanol and formaldehyde, which certainly should occur, at least in expt 1 and 2 where the ozonation was carried essentially to completion. In expt 3 (Table I) the ozonation was not carried to completion and the ozone/amine ratio was equal to the value described by eq 17. The minor products, di-*t*-butyl peroxide, *t*-butyl chloride, and isobutylene most likely arose from ozonation of *t*-butyl hydroperoxide[10] (eq 15) and/or action of chlorine (eq 11) or traces of hydrogen chloride on di-*t*-butyl nitroxide.[9,11]

Another possible route to the nitrobutane (X) not involving di-*t*-butyl nitroxide (VIII) is represented by eq 18 and 19. This is thought to be less likely than the route represented by eq 14 and 15, however, because the blue color of the nitrosobutane (XVII) was never evident during the ozonation. In contrast, the nitrosoalkane color was strongly present during ozonation of *t*-butylamine.[1]

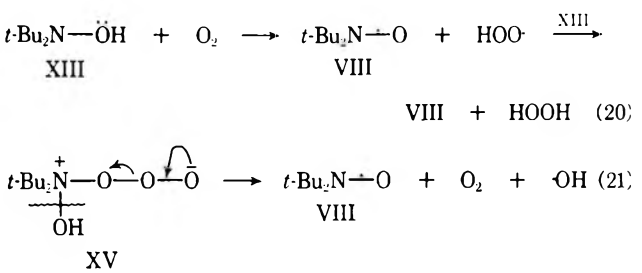


In an attempt to test the validity of reactions such as those of eq 14, 15, 18, and 19, di-*t*-butylhydroxylamine (XIII) was synthesized and ozonized. The results, which are reported in the accompanying paper,[9] were inconclusive owing to the great ease with which the hydroxylamine (XIII) was converted to di-*t*-butyl nitroxide (VIII) by means of oxygen, during the ordinary scale reaction, probably *via* reaction 20. Even during transfer to the ozonation vessel, the red color of di-*t*-butyl nitroxide appeared in the freshly distilled hydroxylamine. The color deepened during the ozonation, and the nitroxide was an isolable product at the end of the ozonation. Even though ozone–nitrogen rather than ozone–oxygen was employed, molecular oxygen would be present throughout the ozonation, from reactions 11, 15, and/or 18 and 19. The hydroxylamine (XIII) appears to be more reactive toward oxygen than toward ozone and, when in excess, would be expected to react with oxygen rather than ozone. Thus, we believe that considerable amounts of the hydroxylamine was converted to the nitroxide, causing the products of ozonation of the hydroxylamine, and ratios thereof, to be similar to those obtained by ozonation of the nitroxide (VIII). The situation would be quite different, however, during ozonation of di-*t*-butylamine (VIII) when the hydroxylamine (XIII) is a minor intermediate. There ozone would always be in excess both to the hydroxylamine and oxygen, and reactions such as 14 and 15 or 18 and 19 should be predominant. Another possible reaction of the hydroxylamine with ozone is shown by eq 21. Evidence that

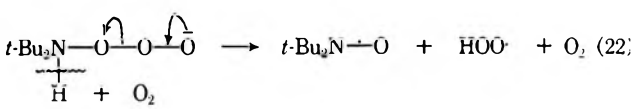
(10) D. Barnard, G. R. McSweeney, and J. F. Smith, *Tetrahedron Lett.*, No. 14, 1 (1960).

(11) (a) A. K. Hoffmann and A. T. Henderson, *J. Amer. Chem. Soc.*, **83**, 4671 (1961); (b) A. M. Feldman, private communication.

ozone does not convert the hydroxylamine (XIII) to the nitroxide (VIII), however, was obtained by following the ozonation, by epr, in methylene chloride at −90° in a small-scale reaction. As ozone–nitrogen was passed into the reaction mixture, the nitroxide signal decreased in intensity or disappeared. Furthermore, eq 21 does not satisfy the stoichiometry of the di-*t*-butylamine ozonation which requires a route to the nitrobutane not involving the nitroxide (VIII).



When di-*t*-butylamine was ozonized in chloroform with ozone–oxygen (expt 4, Table I) rather than with ozone–nitrogen, a slightly lower ratio of ozone to amine reacting, higher yields of 2-methyl-2-nitropropane (X) and *t*-butyl alcohol (XI) and a lower yield of di-*t*-butylammonium chloride (Vab) were obtained. To say the least, this is further evidence against the nitrogen cation radical route to the ammonium salt (eq 3–5); the presence of oxygen does not affect the salt yield appreciably during ozonation of *t*-butylamine in chlorinated solvents. A possible explanation is a competition between the reactions of eq 7 and 22, in which oxygen is com-



peting with unreacted amine for the hydrogen of the amine–ozone adduct. The slightly lower ozone to amine ratio could be due to reaction of the minor di-*t*-butylhydroxylamine (XIII) intermediate with molecular oxygen rather than ozone, as already discussed (eq 20).

A final observation is that higher yields of 2-methyl-2-nitropropane (X) and *t*-butyl alcohol (XI) and a lower yield of di-*t*-butylammonium chloride (Vab) were obtained from ozonation of di-*t*-butylamine in methylene chloride, expt 5, compared with ozonation in chloroform. It is possible that this reflects a lower susceptibility of methylene chloride than chloroform to nucleophilic attack by the oxygen anion radical (eq 8).

Experimental Section

Materials.—Di-*t*-butyl nitroxide (VIII) was prepared by the procedure of Hoffmann *et al.*,[6] bp 58° (11 mm). Di-*t*-butylamine (VII) was made by reduction of di-*t*-butyl nitroxide by the general iron–hydrochloric acid method of Johnson and Degering[12] for reduction of nitro compounds: 46% yield, bp 119°,[13] n^{25}D 1.4100; nmr peak at τ 8.85. di-*t*-Butylhydroxylammonium chloride (mp 175°) and di-*t*-butylhydroxylamine (XIII) were made by sodium reduction of di-*t*-butyl nitroxide, as described previously.[6] 2-Methyl-2-nitropropane[14] (X) and 2-methyl-2-nitrosopropane[15] (XVII) were prepared by known literature procedures.

General Equipment and Procedures.—The ozonation setup and procedures, using ozone–oxygen or ozone–nitrogen and the method for determining molecular oxygen yields are described in earlier papers.[16] A Beckman IR-5A double-beam spectrophotometer was employed for infrared measurements.

Epr Procedures.—All spectra were recorded with a Varian Associates V-4502 spectrometer equipped with a Varian field dial and a 9-in. magnet using a modulation frequency of 100 kcps. The spectra were taken while bubbling an ozone–nitrogen stream (see above) into a special reactor made by sealing off a 25-cm length of 5-mm Pyrex tubing, blowing a bubble midway to prevent the sample from being blown out, and equipping it with a gas inlet tube made by pulling 7-mm glass tubing to capillary size and of such length that the tip came within 1 cm of the bottom of the reaction tube. For reactions in solvents with a high dielectric constant (methylene chloride), the lower part of the reaction tube was only 3 mm in diameter. The reaction mixture consisted of a 1:10 by volume mixture of the amine in pentane, Freon 11 (CCl_2F_2), or methylene chloride; enought to fill 5 cm of the reaction tube was employed. Ozonations were carried out at −120° (pentane, Freon 11) and −90° (methylene chloride), and the epr spectra recorded.

Glpc determinations were made with a Varian Aerograph 1520B chromatograph equipped with flame ionization detectors and a Beckman recorder and integrator. A 10-ft, 1/8-in. column of 20% Carbowax 20 *M* on acid-washed Chromosorb G was used. For determinations of isobutene, acetone, *t*-butyl alcohol, *t*-butyl chloride, 2-methyl-2-nitrosopropane, and di-*t*-butyl peroxide, a temperature of 75° and a flow rate of 20 ml/min was used; benzene was the internal standard for runs in chloroform, whereas toluene was used for the methylene chloride run. Di-*t*-butyl nitroxide and di-*t*-butylhydroxylamine were determined at 95 or 110° and 2-methyl-2-nitropropane at 125° with *p*-xylene as the internal standard, all other conditions remaining the same.

Ozonation of *t*-Butylamine. (A) **Epr Studies.**—Solutions of *t*-butylamine in methylene chloride and in pentane were ozonized at −90 and −120°, respectively, and epr spectra were taken during the ozonations as described above. The characteristic singlet for the ozonate anion radical, with a *g* value of 2.1017,[5] immediately appeared. No other radical was observable. When ozonation was discontinued with the methylene chloride reaction mixture, the singlet rapidly disappeared. When the ozonation in methylene chloride was carried out at −78°, a five-line epr spectrum was observed. The outer lines were 15.5 G from the center line (which was larger than the others), and the two inner lines were 10.5 G from the center line. After the sample had remained at room temperature for 1 day, only a triplet with lines of equal intensity and splittings of 15.5 G was observed. The five-line spectrum therefore consisted of two triplets. The triplet with a splitting constant of 15.5 G was identified as that of di-*t*-butyl nitroxide by comparison of its spectrum with that of an authentic sample.[6,11a,17] The other triplet, which had a half-life of about 70 min at room temperature, was not identified. Similar results were obtained from ozonation of *t*-butylamine in carbon tetrachloride at −20°. From ozonation of *t*-butylamine in isobutane at −78°, however, two overlapping triplets were observed, one for di-*t*-butyl nitroxide with the splitting of 15.5 G and the other, thought to be for the 2-methyl-2-nitropropane anion radical, with a splitting of 26.4 G.[17] When the reaction mixture was allowed to come to room temperature, the signal for the nitropropane anion radical disappeared, and four new lines emerged with two on each side of the center peak, 8 and 24 G from it. These were not identified.

(B) **Ozonation of *t*-butylamine in methylene chloride** at −95° gave a reddish solution which faded rapidly. Upon ozonation in *pentane* at −120°, however, the red color deepened as the ozonation progressed, and a red precipitate formed. When the temperature was allowed to rise to −90°, the red precipitate and color rapidly disappeared.

Ozonation of Di-*t*-butylamine (VII). (A) **Epr Studies.**—Epr spectra of solutions of di-*t*-butylamine in methylene chloride at −90°, Freon 11 at −115°, and pentane at −120° all showed

(12) K. Johnson and E. F. Degering, *J. Amer. Chem. Soc.*, **61**, 3194 (1939).
(13) F. Klages and H. Sitz, *Ber.*, **92**, 2606 (1959).
(14) N. Kornblum, R. J. Clutter, and W. J. Jones, *J. Amer. Chem. Soc.*, **78**, 4003 (1956).
(15) W. D. Emmons, *ibid.*, **79**, 6522 (1957).
(16) A. M. Reader, P. S. Bailey, and H. M. White, *J. Org. Chem.*, **30**, 784 (1965), and references therein.
(17) A. K. Hoffman, W. G. Hodgson, and W. H. Jura, *J. Amer. Chem. Soc.*, **83**, 4675 (1961); see also references in footnote 7.

weak signals for the di-*t*-butyl nitroxide radical (VIII). As soon as ozone was passed into the solutions, by the technique already described, the signals greatly increased. Shortly thereafter signals for the 2-methyl-2-nitrobutane anion radical[17] also appeared (see description under *t*-butylamine ozonation above) very weakly in the methylene chloride reaction mixture but of moderate intensity in the other two solutions. No signal for the ozonate anion radical was observed in any of these reaction mixtures. However, when a 1:4 mixture of *t*-butyalmine and di-*t*-butylamine in pentane was ozonized at −120° by the above technique, a strong signal for the ozonate anion radical[5] (see description under ozonation of *t*-butylamine, above) immediately appeared along with a weaker signal for the di-*t*-butyl nitroxide radical. *t*-Butylamine appears to be more reactive toward ozone than di-*t*-butylamine. Ozonation of di-*t*-butyl nitroxide in pentane at −120° resulted in a decrease in the nitroxide triplet, but no formation of the 2-methyl-2-nitropropane anion radical signal. Epr spectra of solutions of di-*t*-butylhydroxylamine in methylene chloride, pentane, and Freon 11 at −90° all showed signals for the di-*t*-butyl nitroxide radical (VIII). When ozone–nitrogen was introduced into the solution, the signal weakened in intensity or disappeared (in case of CH_2Cl_2).

(B) **Product Determination.**—In a typical experiment, a solution of 2.36 mmol of di-*t*-butylamine (VII) in 15 ml of chloroform was ozonized at −60° with an ozone–nitrogen stream containing 6.5 mmol of ozone. The amount of ozone reacting was determined by titrating the iodide trap and subtracting the amount found there from the total amount of ozone employed. A cold trap following the reaction vessel in the reaction train contained no products after the ozonation. The reaction mixture gave a positive iodide test for peroxide but a negative lead tetraacetate test for hydroperoxide.[18] Determinations of the liquid products were by glpc (see above). Di-*t*-butylammonium chloride was determined by evaporation of an aliquot of the reaction mixture to dryness and weighing the vacuum-dried residue. It was identified by comparison of its ir spectrum (Nujol mull) with that of an authentic sample; the ir spectrum also showed the absence of di-*t*-butyl hydroxylammonium chloride. The results are shown in Table I (expt 1). In another experiment the ozonation was not carried to completion. The di-*t*-butylammonium chloride was extracted from the reaction mixture with water and determined by titration for chloride with standard silver nitrate solution. Ethereal hydrogen chloride was then added to the organic layer; evaporation and determination of the residue by weighing gave the yield of unreacted di-*t*-butylamine.

Reactions of *t*-Butylamine and Di-*t*-butylamine with Phosgene in Chloroform at −65°.—Phosgene was passed into a solution of 0.5 ml of *t*-butylamine in 8 ml of chloroform at −65° for several minutes. An ir spectrum of the reaction mixture showed a strong isocyanate peak (2270 cm^{-1}) but no urea peak. Addition of *t*-butylamine to the reaction mixture at room temperature eliminated the isocyanate peak and gave rise to a strong urea carbonyl peak (1630 cm^{-1}). Passage of phosgene into a chloroform solution of di-*t*-butylamine under the same conditions gave no appreciable reaction, as indicated by ir spectra.

(18) R. Criegee, H. Pilz, and H. Flygare, *Ber.*, **72**, 1799 (1939).

Registry No.—VII, 21981-37-3.

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Ozonation of Amines. V.[1] Di-*t*-butyl Nitroxide

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Ozonation of di-*t*-butyl nitroxide occurs with ease giving 2-methyl-2-nitropropane and tri-*t*-butyl nitroxide as the major initial products. Ozonation of tri-*t*-butyl nitroxide gives 2-methyl-2-nitropropane, *t*-butyl alcohol, and acetone as major products. Minor products of the ozonations are 2-methyl-2-nitrosopropane, isobutene, di-*t*-butyl peroxide, and (in chloroform solution) *t*-butyl chloride and di-*t*-butylhydroxylammonium chloride. Reaction mechanisms are proposed, involving initial electrophilic ozone attacks on the nitroxides.

In earlier papers we have reported the detection of the stable radical di-*t*-butyl nitroxide[2] among the products of ozonation of *t*-butylamine[1,3] and di-*t*-butylamine.[1] The present paper deals largely with a study of the ozonation of this interesting stable radical, but also discusses briefly the source of the material in the above mentioned ozonations.

Di-*t*-butyl nitroxide appears to be only a minor byproduct in the ozonation of *t*-butylamine;[1,3] although it was detected by epr in ozonations carried out at −78° or higher, the only radical signal observed during ozonations carried out at −90° or below was that for the ozonate anion radical.[1] Other products obtained in trace amounts from ozonation of *t*-butylamine in chloroform were *t*-butyl alcohol, acetone, and isobutane.[3] Two sources of di-*t*-butyl nitroxide during the reaction between sodium metal and 2-methyl-2-nitropropane (I) have been suggeted.[2] One involves hydrolysis of a salt, thought to be sodium di-*t*-butylhydroxylamine oxide and formed by attack of *t*-butyl radicals upon the initially formed 2-methyl-2-nitropropane anion radical (eq 3); the *t*-butyl radicals arose from decomposition of the nitroalkane anion radical (eq 2). The other source involved attack of *t*-butyl radicals on 2-methyl-2-nitrosopropane (eq 5). Either or both of these routes could also be the source of di-*t*-butylnitroxide during ozonation of *t*-butylamine. A major product is 2-methyl-2-nitropropane[3] (I), and it

(1) For paper IV of this series, see P. S. Bailey, J. E. Keller, and T. P. Carter, Jr., *J. Org. Chem.*, **35**, 2777 (1970).

(2) A. K. Hoffmann, A. M. Feldman, E. Gelblum, and W. G. Hodgson, *J. Amer. Chem. Soc.*, **86**, 639 (1964).

(3) P. S. Bailey and J. E. Keller, *J. Org. Chem.*, **33**, 2680 (1968).

$$\cdot\bar{O}_3 + \underset{\textbf{I}}{t\text{-BuNO}_2} \longrightarrow O_3 + \underset{\textbf{II}}{t\text{-BuNO}_2^{\dot{-}}} \qquad (1)$$

$$\underset{\textbf{II}}{t\text{-BuNO}_2^{\dot{-}}} \longrightarrow t\text{-Bu}\cdot + NO_2^- \qquad (2)$$

$$t\text{-Bu}\cdot + \underset{\textbf{II}}{t\text{-BuNO}_2^{\dot{-}}} \longrightarrow t\text{-Bu}_2NO_2^- \xrightarrow{\text{HOH}} \underset{\textbf{III}}{t\text{-Bu}_2N\dot{-}O} + \cdot OH + OH^- \qquad (3)$$

$$t\text{-Bu}\dot{N}\overset{+}{H}_2 \longrightarrow t\text{-Bu}\cdot + \cdot\underset{+}{\dot{N}}H_2 \qquad (4)$$

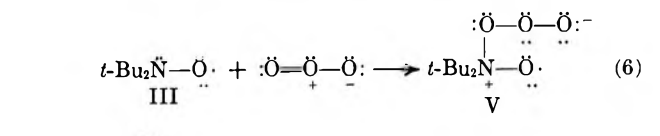
$$t\text{-Bu}\cdot + \underset{\textbf{IV}}{t\text{-Bu}\ddot{N}{=}\ddot{O}:} \longrightarrow \underset{\textbf{III}}{t\text{-Bu}_2N\dot{-}O} \qquad (5)$$

could conceivably be converted to the corresponding anion radical (II) by the ozonate anion radical (eq 1). Water is a minor product of the ozonation of *t*-butylamine.[3] However, a major intermediate in the ozonation of *t*-butylamine is 2-methyl-2-nitrosopropane[3] (IV). The source of *t*-butyl radicals necessary to convert it to di-*t*-butyl nitroxide (eq 5) could either be as described above, or else decomposition of the *t*-butylamine cation radical (eq 4). The occurrence of trace amounts of acetone, *t*-butyl alcohol, and isobutane among the products of ozonation of *t*-butylamine[3] is also indicative of the production of *t*-butyl radicals during the ozonation, although the first two of these could also arise from ozonation of di-*t*-butyl nitroxide, as will be seen.

Di-*t*-butyl nitroxide (III) was shown to be an initial product in the ozonation of di-*t*-butylamine.[1] Similar nitroxides have also been reported to be not only initial, but also major products of ozonation of certain aromatic and alicyclic secondary amines.[4] Because of this it was most important to study the ozonation of di-*t*-butyl nitroxide and to compare the results with those of the ozonation of di-*t*-butylamine.[1]

The ozonation of di-*t*-butyl nitroxide was carried out in chloroform at −65°, carbon tetrachloride at −20°, and toluene at −78° with an ozone–nitrogen stream containing 1.0 to 2.2 mol equiv of ozone. The results are shown in Table I. The major product in all cases was 2-methyl-2-nitropropane (I). Only in those cases where the ozonation was not carried out to completion (all of the di-*t*-butyl nitroxide used) was any 2-methyl-2-nitrosopropane (IV) a product. The *t*-butyl group lost in the formation of the nitroalkane (I) was found in the products largely in the forms of *t*-butyl alcohol (VIII), acetone (IX), and tri-*t*-butyl nitroxide (VI). The latter was detected, however, only in those cases where ozonation was not carried to completion. Minor products were di-*t*-butyl peroxide, isobutene, *t*-butyl chloride, and di-*t*-butylhydroxylammonium chloride; the last two, of course, were obtained only from ozonations in chloroform and/or carbon tetrachloride.

We suggest eq 6–13 as a description of the route to the major products from ozonation of III in chloroform solution. Summed together these give eq 14.



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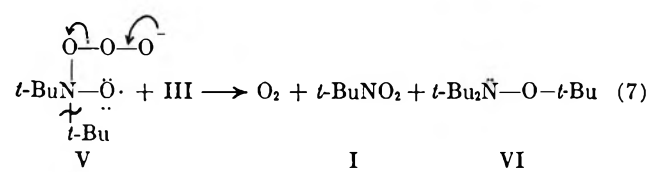

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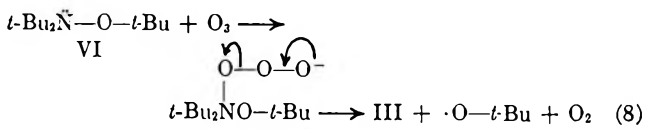

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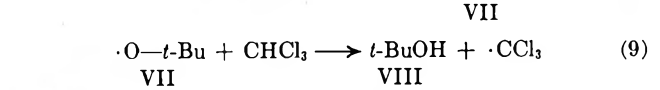

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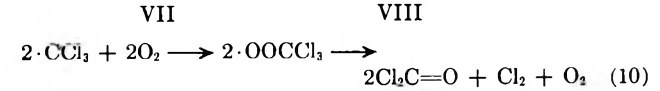

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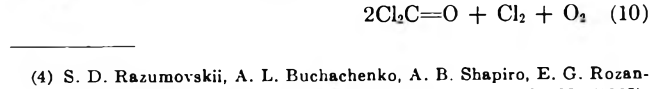
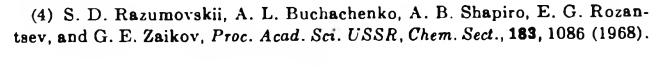


(11)



(12)

(13)

(14)

Since di-*t*-butyl nitroxide (III) is very reactive toward ozone, which is diamagnetic, we suggest that in the initial reaction III behaves as a nucleophile (eq 6) rather than a radical, just as do amines. Interaction of the nitroxide–ozone adduct (V) with another molecule of the nitroxide should give 3-methyl-3-nitropropane (I), the major product of the ozonation, and tri-*t*-butyl nitroxide (VI). Di-*t*-butyl nitroxide is known to be a vigorous free-radical scavenger; its reaction with *t*-butyl radicals to give tri-*t*-butyl nitroxide occurs with great ease.[2] Evidence that VI is an initial product of the ozonation is that the yield decreased significantly as the amount of ozone employed increased (*cf.* experiments 1, 2, and 4–6). The tri-*t*-butyl nitroxide (VI) is quite reactive toward ozone, although not so reactive as is di-*t*-butyl nitroxide (III). Ozonation of the tri-*t*-butyl nitroxide (VI) in a separate experiment gave the same products as obtained from ozonation of di-*t*-butyl nitroxide, as predicted by eq 8–11. Due to the greater reactivity of the di-*t*-butyl nitroxide (III), however, only weak epr signals for III were detected in the mixture. Reaction 10 has previously been suggested by Cadogan, *et al.*[5]

The major reaction course for ozonation of di-*t*-butyl nitroxide gives no explanation for the minor products 2-nitroso-2-methylpropane (IV), di-*t*-butylhydroxylammonium chloride, isobutene, *t*-butyl chloride, and di-*t*-butyl peroxide. The latter one probably arises from a minor fate of the *t*-butoxy radicals (VII) obtained in reaction 8. The others appear to arise, at least largely, from attack of either chlorine (from eq 10) or hydrogen chloride (possibly from some ozone attack on chloroform) on the starting di-*t*-butyl nitroxide. These are the products reported from such interactions,[6] as has been confirmed in our laboratory. This is, certainly, the most reasonable route to di-*t*-butylhydroxylammonium chloride. It is likely, however that there are alternative routes to the other minor products, since they are also obtained from ozonation of III in carbon tetrachloride; carbon tetrachloride is not appreciably attacked by ozone and reaction 9, of course, is specific for chloroform. This is especially true of isobutene, which is also obtained from the ozonation of III in toluene. It is possible that the *t*-butyl radical released in reaction 7 has some degree of freedom. It so, it could extract chlorine from the medium, to give *t*-butyl chloride, or lose a hydrogen (perhaps to *t*-butoxy radicals) to produce isobutene. A possible alternative route to 2-methyl-2-nitrosopropane (IV) is shown by eq 15, in competition with reaction 7. The *t*-butyl alcohol obtained in carbon tetrachloride solution could arise by abstraction of hydrogen by *t*-butoxy

(4) S. D. Razumovskii, A. L. Buchachenko, A. B. Shapiro, E. G. Rozantsev, and G. E. Zaikov, *Proc. Acad. Sci. USSR, Chem. Sect.*, **183**, 1086 (1968).

(5) J. I. G. Cadogan, D. H. Hey, and P. G. Hibbert, *J. Chem. Soc.*, 3939 (1965).

(6) (a) A. K. Hoffmann and A. T. Henderson, *J. Amer. Chem. Soc.*, **83**, 4671 (1961); (b) A. M. Feldman, private communication.

TABLE I
OZONATIONS OF DI-*t*-BUTYL NITROXIDE AND DI-*t*-BUTYLHYDROXYLAMINE

Expt	Solv[a] (ml)	Compd,[b] —mmol— Starting	Compd,[b] —mmol— Reacting[c]	Ozone[d] —mmol— Passed	Ozone[d] —mmol— Reacted	O_3/compd[e]	O_2 evolved, mmol (%)[f]	*t*-BuNO$_2$, mmol (%)[g]	*t*-BuN=O, mmol (%)[g]	*t*-BuNHOH Cl^-, mmol (%)[g]	*t*-BuOH, mmol (%)[g]	Acetone, mmol (%)[g]	Isobutene, mmol (%)[g]	(*t*-BuO–)$_2$, mmol (%)[g]	*t*-BuCl, mmol (%)[g]	Others, mmol (%)[g]	N,[h] mmol (%)	*t*-Bu,[i] mmol (%)
1	$CHCl_3$ (15)	3.00	3.00	6.5	5.5	1.8	3.2 (58)	2.64 (88)	0 (0)	0.27 (9)	0.93 (31)	0.88 (29)	0.04 (1)	0.07 (2)	0.08 (3)	0 (0)	2.91 (97)	2.34 (78)
2	$CHCl_3$ (15)	3.00	3.00	5.3	5.2	1.7	3.1 (60)	2.74 (91)	0 (0)	0.17 (6)	...[j]	...[j]	...[j]	...[j]	...[j]	0.06[k] [2]	2.91 (97)	...[j]
3	$CHCl_3$ (25)	5.00	5.00	7.5	7.5	1.5	...[j]	4.22 (84)	0 (0)	0.60 (12)	1.30 (26)	1.16 (23)	0.45 (9)	...[j]	0.18 (4)	[j]	4.82 (96)	3.69 (74)
4	$CHCl_3$ (15)	5.00	4.33	5.0	5.0	1.2	3.1 (62)	3.02 (70)	0.46 (11)	0.31 (7)	0.88 (20)	0.63 (15)	0.53 (12)	0.14 (3)	0.30 (7)	0.38[k] (9)	4.17 (96)	3.69 (85)
5	$CHCl_3$ (15)	9.02	4.64	5.0	5.0	1.1	...[j]	...[j]	...[j]	...[j]	...[j]	...[j]	...[j]	...[j]	...[j]	1.28[k] (28)	...[j]	...[j]
6	$CHCl_3$ (6)	2.10	0.43	0.52	0.52	1.2	...[j]	...[j]	...[j]	...[j]	...[j]	...[j]	...[j]	...[j]	...[j]	0.13[k] (30)	...[j]	...[j]
7	CCl_4 (15)	5.00	4.83	5.0	5.0	1.0	3.4 (68)	3.39 (70)	0.37 (8)	...[j]	0.67 (14)	0.46 (10)	0.29 (6)	0.28 (6)	0.06 (1)	0.82[k] (17)	4.58 (95)	3.68 (76)
8	Toluene (15)	5.00	4.21	5.0	5.0	1.2	3.7 (74)	2.92 (69)	...[j]	0	0.91 (22)	0.29 (7)	0.27 (6)	0.08 (2)	0	1.06[k] (25)	3.98 (95)	3.75 (89)
9	$CHCl_3$ (15)	3.00	2.98	3.6	3.6	1.2	2.9 (81)	1.46 (49)	0.14 (5)	0.44 (15)	0.69 (23)	0.47 (16)	0.18 (6)	...[j]	0.49 (16)	0.39[l] (13)	2.43 (81)	2.66 (89)

[a] The ozonations in $CHCl_3$ were carried out at −65°, the one in CCl_4 at −20°, and the one in toluene at −78°. [b] In runs 1–8 the compound ozonized was di-*t*-butyl nitroxide, whereas in run 9 di-*t*-butylhydroxylamine was ozonized. [c] The mmoles of nitrogen compound reacting is equal to mmoles starting compound minus mmoles of same compound detected at end of experiment. [d] All ozonations were with ozone–nitrogen. [e] Ratio of ozone reacting to nitrogen compound reacting. [f] Per cent yield of molecular oxygen is based on mmoles of ozone reacting. [g] Percentage yields of organic products are based on mmoles of starting nitrogen compound which reacted. [h] Per cent accounting of nitrogen in products from starting amine. [i] Per cent accounting in products of second *t*-butyl group (which is lost in production of the nitro compound). [j] Not determined. [k] Tri-*t*-butyl nitroxide. [l] Di-*t*-butyl nitroxide.

radicals from various sources, including *t*-butyl and methoxy radicals.

$$t\text{-Bu}\text{—}\ddot{\underset{\cdot\cdot}{N}}\text{=}\ddot{O}\text{:} \quad + \quad t\text{-Bu}\text{—}O\cdot \quad + \quad O_2 \qquad (15)$$

Experiment 9 of Table I shows the results of ozonation of di-*t*-butylhydroxylamine rather than of di-*t*-butyl nitroxide (III). The products are the same as those obtained from ozonation of di-*t*-butyl nitroxide, although the proportions are different. As discussed in the preceding paper, these results are hard to interpret, but are, at least partially, due to oxidation of the hydroxylamine to the nitroxide by molecular oxygen.

Experimental Section

Materials.—Tri-*t*-butyl nitroxide (VI) was prepared by the procedure of Hoffmann, *et al.*,[2] bp 85° (11 mm). The sources of the other materials were described in the accompanying paper.[1]

General Equipment and Procedures.—The ozonation, epr, glpc, and ir equipment and procedures were adequately described in the accompanying paper.[1] In the glpc procedure, tri-*t*-butyl nitroxide (VI) was determined under the same conditions as was di-*t*-butyl nitroxide (III).[1]

Ozonation of Di-*t*-butyl Nitroxide (III).—The ozonations were carried out exactly as described for di-*t*-butylamine in the accompanying paper.[1] Glpc determinations were carried out as described above and in the accompanying paper.[1] The di-*t*-butylhydroxylammonium chloride was determined by evaporation of the reaction mixture to dryness and weighing the vacuum dried residue; it was identified by comparison of its infrared spectrum with that of an authentic sample. The results are shown in Table I.

Ozonation of Tri-*t*-butyl Nitroxide (VI) was carried out as described for III, above, except that the ozone absorption was slower (some ozone passed into the trap, throughout); the glpc determinations were performed qualitatively. The products were the same as those obtained from ozonation of di-*t*-butyl nitroxide.

In another experiment a microozonation of VI in pentane at −120° was monitored by epr.[7] The di-*t*-butyl nitroxide triplet was present at the beginning of the ozonation but decreased in size and remained weak as ozone was introduced; this indicates that di-*t*-butyl nitroxide is a product of the ozonation, but is more reactive than tri-*t*-butyl nitroxide.

Ozonation of Di-*t*-butylhydroxylamine.—The ozonation was complicated by the ease with which the hydroxylamine was oxidized to di-*t*-butyl nitroxide. It was necessary to purify the hydroxylamine immediately prior to use by washing with cold pentane on a Büchner funnel. The solid was quickly dried under vacuum and was weighed and added to the solvent which had previously been purged with nitrogen for several hours. Oxygen was completely purged from the silica gel column containing the ozone before the reaction vessel was placed in the gas stream. Even then, the pale red color of the nitroxide was present in the reaction mixture and increased during the ozonation. During determination of products the color deepened due to conversion of unreacted amine to nitroxide. The results are shown in Table I, experiment 9. In another experiment a microozonation in methylene chloride at −90° was monitored by epr.[7] The signal for di-*t*-butyl nitroxide was present before the ozonation but disappeared shortly after ozone was introduced. This indicates that the nitroxide is not a product of reaction of ozone with di-*t*-butylhydroxylamine.

(7) See technique described in accompanying paper.[1]

Reaction of Di-*t*-butyl Nitroxide (III) with Hydrogen Chloride and Chlorine.—A solution of 0.1 g of di-*t*-butyl nitroxide in 2.5 ml of chloroform was treated with gaseous hydrogen chloride at −65,° after which the reaction mixture was taken out of the cooling bath. The color of the reaction mixture turned from red to green to blue. A qualitative glpc determination of products, as described for the ozonation experiments, showed isobutene, *t*-butyl chloride, and 2-methyl-2-nitrosopropane. Evaporation of the solution left a solid which was identified as di-*t*-butylhydroxylammonium chloride by its ir spectrum. Similar results were obtained upon similar treatment of di-*t*-butyl nitroxide with chlorine.

Registry No.—III, 2406-25-9; di-*t*-butylhydroxylamine, 10531-39-2; VI, 4432-73-9.

Acknowledgment.—This work was supported by grants from the National Science Foundation (GP-7351) and the Robert A. Welch Foundation (F-042), for which the authors are very grateful. They also thank Mr. Thomas P. Carter, Jr., for carrying out two of the ozonations.

Addition of Dinitrogen Trioxide to Nonconjugated Dienes

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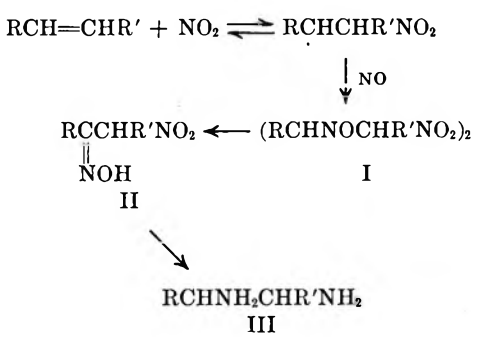
Received September 15, 1969

The addition of dinitrogen trioxide is shown to proceed selectively at the bicyclic double bond of dicyclopentadiene. Simple adduct formation without transannular reaction occurs with 1,5-cyclooctadiene; however, norbornadiene undergoes considerable transannular addition to give nortricyclene derivatives. Reduction of the adducts leads to hydroxylamino oxime derivatives and diamines. The course of addition of nitrogen oxides is interpreted by a free-radical pathway.

The reaction of olefins with dinitrogen trioxide or with a mixture of nitrogen oxides to form 1:1 adducts is a classical technique of introducing two vicinal carbon–nitrogen bonds into an olefinic system.[2a] The adducts, known as pseudonitrosites, are usually 2-nitronitroso dimers I which can be thermally rearranged to the more soluble α-nitroximes II, and subsequently reduced to vicinal diamines III. The addition of dinitrogen trioxide is believed to involve reversible attack of nitrogen dioxide on olefin with the formation of a free-radical intermediate containing a carbon–nitrogen bond which can combine with nitric oxide and dimerize, resulting in the adduct **1**.[2b,c]



It was of interest to determine whether the formation of these adducts from cyclic, nonconjugated dienes occurs selectively and whether transannular reactions take place. Dicyclopentadiene, 4-vinylcyclohexene-1, 1,5-cyclooctadiene, and norbornadiene were selected as cases for study. The results are in no disagreement with a free-radical mechanism and are interpreted accordingly.

Dicyclopentadiene–N_2O_3.—Dicyclopentadiene was reported to form a pseudonitrosite in 1908;[3] however, the structure of dicyclopentadiene was unknown at that time, and consequently the structure proposed for the adduct was incorrect. Examination of the nmr spectrum reveals that one double bond manifested as a singlet at δ 5.0 ppm (in $CDCl_3$) is present. Cyclopentene exhibits a singlet at δ 5.7 ppm, whereas the bicyclic double bond in norbornene and in dicyclopentadiene is observed as an unsymmetrical triplet at δ 6.0 ppm. The singlet character and relative upfield position of the olefinic signal would suggest a cyclopentenyl rather than a norbornenyl double bond. Furthermore, the presence of a bicyclic double bond affects the chemical shift of the bridge protons; the 7s and 7a protons in norbornene and dicyclopentadiene show absorption patterns in the area of δ 1–1.5 ppm, whereas the spectrum of the pseudonitrosite possesses no signals in this region. A competition experiment involving a mixture of norbornene and cyclopentene with a limited quantity of nitrogen oxides results in almost exclusive consumption of the norbornene and formation of norbornene pseudonitrosite[4] rather than the cyclopentene derivative, indicating that a norbornenyl bicyclic double bond is intrinsically more reactive toward nitrogen oxides than is a cyclopentene system.

It is likely that the products are derived chiefly from *exo-cis* addition as in the case of norbornene,[4] but in this case there is less certainty. There are two *exo-cis* addition products for dicyclopentadiene IV and IVa, differing in the position of the double bond, and at least three types of dimers possible: dimers of IV and IVa, and the mixed dimer of IV and IVa, as well as *cis*- and *trans*-nitroso dimer forms, *i.e.*, geometric isomers *cis* and *trans* with respect to the nitrogen–nitrogen bond. Isomerization to the nitroxime affords a product whose nmr spectrum reveals a doublet of area 1 at δ 4.8 ppm, attributable to the highly shielded proton attached to the carbon atom bearing the nitro group. The 2-cps coupling reflected also in the signal assigned to the 7-*anti* bridge hydrogen at δ 1.8 ppm suggests that the 3 proton lies in an *endo* position, as in the case of norbornene nitroxime.[4] The nitroxime most likely

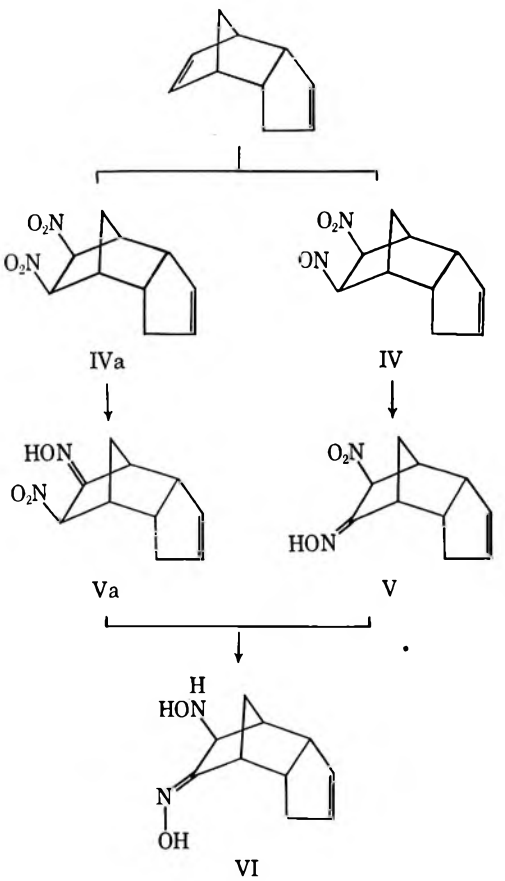
(1) Department of Chemistry, East Tennessee State University, Johnson City, Tenn.

(2) (a) H. Wieland, *Justus Liebigs Ann. Chem.*, **424**, 71 (1920); (b) H. Schechter, *Rec. Chem. Progr.*, **25**, 55 (1964); (c) M. L. Scheinbaum, *Amer. Chem. Soc. Petrol. Chem., Prepr.*, **13**, 193 (1968).

(3) (a) H. Wieland and H. Stenzel, *Justus Liebigs Ann. Chem.*, **360**, 299 (1908); (b) A. Rule, *J. Chem. Soc.*, **93**, 1508 (1908).

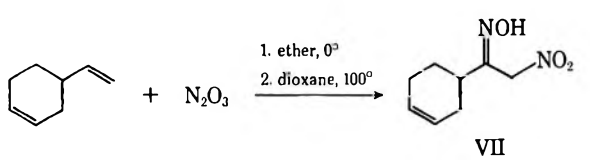
(4) M. L. Scheinbaum, *J. Org. Chem.*, **33**, 2586 (1968).

consists of a mixture of V and Va with the nitro group predominately in the *exo* position. Hydrogenation in the presence of palladium–carbon catalyst affords a single product, the hydroxylamino oxime VI. Attempts to effect catalytic reduction to the diamine were unsuccessful, probably owing to steric hindrance to the approach of hydrogen.



The selectivity of addition of nitrogen oxides to the bicyclic double bond of dicyclopentadiene is not particularly remarkable in that preference for this site is observed in the reactions of dicyclopentadiene with a variety of reagents.[5] What is significant is that dicyclopentadiene–dinitrogen trioxide monoadduct is readily obtained in high yield. Pseudonitrosites and other types of nitroso dimers are ordinarily poorly soluble species, so that monoadducts rapidly crystallize out of solution and are probably less prone to react at the free double bond to form diadducts in their crystalline form than is an olefin in solution.

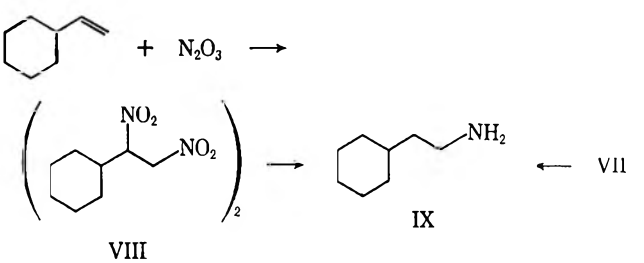
4-Vinylcyclohexene–N_2O_3.—Addition of dinitrogen trioxide to 4-vinylcyclohexene results in a low yield of adduct that readily rearranges to the nitroxime. The nmr spectrum of the latter possesses signals corresponding to two olefinic protons and two nitromethylene protons; vinyl absorption is absent. The spectrum is in accord with structure VII derived from addition to the



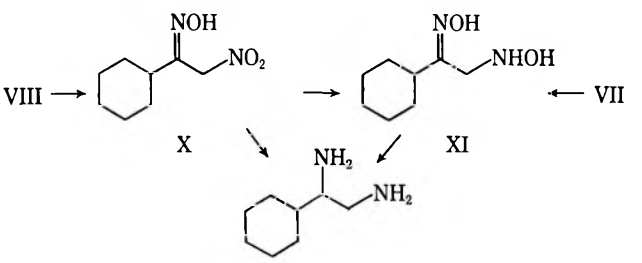
(5) P. Wilder Jr., C. F. Culberson, and G. T. Youngblood, *J. Amer. Chem. Soc.*, **81**, 655 (1959).

vinyl double bond. Since there is no change in the nature of unreacted starting material during the course of reaction, there is little reason to anticipate alteration in the position of the ring double bond.

The dinitrogen trioxide adduct of vinylcyclohexane (VIII) was prepared and characterized. The nmr spectrum resembles that of propylene pseudonitrosite[2b] with an ABC portion of an ABCX pattern for protons attached to nitrogen bearing carbon atoms. Reduction of this derivative with lithium aluminum hydride results in loss of nitrogen to give the same amine, 2-cyclohexylethylamine (IX), as obtained by high pressure, Raney nickel catalyzed hydrogenation of VII at



75°. The pseudonitrosite VIII is isomerized to the nitroxime X on treatment with refluxing dioxane. Hydrogenation of X with palladium-on-carbon catalyst affords the same hydroxylamino oxime XI as obtained from similar catalytic reduction of VII. Lithium aluminum hydride reduction or Raney nickel catalyzed, high-pressure hydrogenation of either X or XI affords the vicinal diamine XII. Since the reaction of N_2O_3 with vinylcyclohexane is straightforward, the matching of reduction products confirms the structure of VII as stemming from addition to the vinyl double bond.

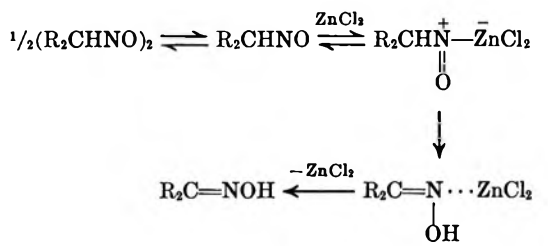


Selectivity of free-radical reactions toward the vinyl double bond of 4-vinylcyclohexene has been reported for a variety of reagents;[6] however, polar reagents often attack preferentially at the cyclohexene bond.[7] That the selective isolation of VII in the case of nitrogen oxide addition is not attributable to any special intrinsic reactivity of vinyl groups as opposed to cyclohexene double bonds is borne out by competition experiments. Cyclohexene is consumed about three times more rapidly than vinylcyclohexane, and 4-vinylcyclohexene reacts at a rate intermediate between the two. Probably, mostly ring attack does occur with 4-vinylcyclohexene-1, but crystallization of the vinyl adduct is preferred. This is attributable either to slow rates of recrystallization of the ring derivatives or to their susceptibility to undergo secondary reactions leading to soluble products, such as nitro olefins, nitro ketones, nitro nitrites,

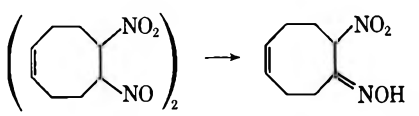
(6) R. H. Fish, H. G. Kuivila, and I. J. Tyminski, *ibid.*, **89**, 5861 (1967).
(7) R. H. Perry, Jr., and B. G. Cornan, *Amer. Chem. Soc. Div. Petrol. Chem., Prepr.*, **12**, D5 (1967).

or dinitro compounds. The dimer which actually does crystallize, that derived from addition to the vinyl group, is obtained in only 11% yield.

1,5-Cyclooctadiene–N_2O_3.—1,5-Cyclooctadiene is known to form a monoadduct with dinitrogen trioxide.[8] Nmr examination of the crude product indicates that one double bond is retained. No isomerization of unreacted diene is observed during the course of reaction, suggesting that the position of the double bond is unchanged in the adduct XIII. Isomerization of 1,5-cyclooctadiene pseudonitrosite does not occur readily; exposure of the pseudonitrosite to refluxing dioxane results in partial recovery of the starting material along with decomposition and tar formation. Isomerization is best carried out in alcoholic solution in the presence of catalytic quantities of a transition metal salt, such as zinc chloride. The zinc ion probably coordinates with the nitroso group, rendering the adjacent proton more activated toward rearrangement. The technique also works for rearranging other stubborn nitroso compounds, *e.g.*, cyclohexene pseudonitrosite undergoes rearrangement to 2-nitrocyclohexanone oxime.

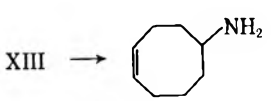


The nitroxime derived from XIII exhibits nmr signals for two olefinic protons as well as nitromethine and oxime protons. The spectrum is in accord with structure XIV; no evidence of transannular reaction is observed.



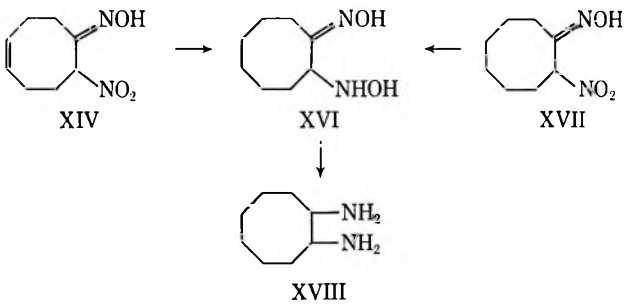
XIII XIV

Lithium aluminum hydride reduction of XIII occurs with loss of a nitrogen functionality to give the unsaturated amine XV, which can be further reduced to cyclooctylamine.



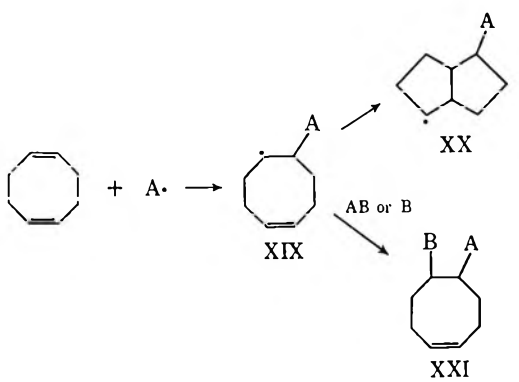
XV

Hydrogenation of the nitroxime XIV with palladized carbon catalysis affords 2-hydroxylaminocyclooctanone oxime (XVI). The same derivative is formed by similar reduction of 2-nitrocyclooctanone oxime (XVII)[8] which is derived from cyclooctene through dinitrogen trioxide addition and isomerization. The preparation of XVI from either XV or XVII confirms the nmr assignment of XIII as a simple 1,2 adduct rather than a transannular product. The hydroxylamino oxime XVI can be reduced by lithium aluminum hydride or catalytically to a mixture of *cis*- and *trans*-1,2-diaminocyclooctanes (XVIII).



XIV XVI XVII XVIII

Although free-radical addition reactions of 1,5-cyclooctadiene leading to bicyclo[3.3.0]octane derivatives have been reported for a variety of reagents, only simple 1,2 adducts were observed in the addition of thiolacetic acid, thiolbenzoic acid, and benzenethiol to 1,5-cyclooctadiene.[9] The following explanation was used to rationalize the absence of transannular product in low-temperature addition of trimethyl tin hydride.[9] In the absence of a good radical donor, the intermediate radical XIX can undergo rearrangement to the bicyclic radical XX resulting in formation of transannular product. If a good B donor is present, such as a thiol, simple 1,2 addition to give XXI occurs more rapidly than formation of XX. This concept of free-radical addition to 1,5-cyclooctadiene turns out to be applicable in the present case where AB is dinitrogen trioxide. The radical donor B is nitric oxide, a well-known free-radical trapping agent which is in relatively high concentration under the reaction conditions. Consequently, only the 1,2-addition product is obtained. The activation energy required to rearrange XIX to XX when A = NO_2 is evidently too high relative to the lifetime of XIX in the presence of nitric oxide. Transannular reaction has not been reported for free-radical additions to dicyclopentadiene or 4-vinylcyclohexene-1, and was not observed with dinitrogen trioxide.



XIX XX XXI

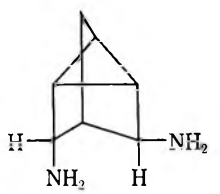
Norbornadiene–N_2O_3.—Norbornadiene reacts with nitrogen oxides to form a tan-colored N_2O_3 adduct which undergoes considerable decomposition to tarry products on attempted rearrangement or recrystallization in hot solvents. Nmr examination of the adduct indicates that olefinic absorption is only 30–40% as strong as expected for simple N_2O_3 addition to one double bond;

(8) D. Klamann, W. Koser, P. Weyerstahl, and M. Fligge, *Chem. Ber.*, **98**, 1831 (1965).

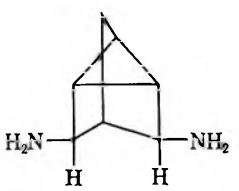
(9) J. M. Locke and E. W. Ducke, *Chem. Commun.*, 151 (1965).

apparently considerable transannular reaction to saturated products takes place.

High-pressure hydrogenation with Raney nickel converts the crude adduct to a tarry mixture which on distillation affords a mixture of diamines. Vpc inspection reveals two major components in a ratio of 3:2, and nmr examination of the crystalline dihydrochlorides indicates that these diamines are *trans*- and *exo-cis*-3,5-diaminonortricyclene (XXII and XXIII). Separation of the two isomers is achieved by conversion to the diacetamides. The diacetamide of the major isomer XXII is more soluble than that of XXIII so that the latter can be fractionally crystallized. Failure to form a cyclic urea on treatment of the diamine mixture with phosgene suggests that the *cis-endo* isomer is not present.



XXII



XXIII

Transannular reaction is more favored in the case of norbornadiene than in that of 1,5-cyclooctadiene. The formation of nortricyclene addition products is generally encountered in free-radical reactions of norbornadiene.[10] The radical intermediate XXIV formed by either *endo* or *exo* attack of nitrogen dioxide is geometrically well set up for conversion to a tricyclic radical XXV which combines with nitric oxide to form a 3,5-disubstituted nortricyclene.

XXIV XXV

Experimental Section

Ir spectra were taken on a Beckman IR-5; nmr spectra with a Varian A-60, using TMS as internal reference. Melting points are uncorrected. Elemental analyses and molecular weight determinations were performed by Galbraith Laboratories.

Dicyclopentadiene Pseudonitrosite (IV and IVa).—A stirred solution of 132 g (1 mol) of dicyclopentadiene in 500 ml of 1:1 pentane–ether solution at 0° was treated with a stream of 2:1 nitric oxide–air until unabsorbed, brown nitrogen dioxide could be observed above the surface of the reaction mixture. The product was filtered, washed with ether, and dried to give 170 g (82% yield) of crude adduct. Two recrystallizations from methylene chloride–pentane afforded white crystals: mp 151–154°; nmr ($CDCl_3$) δ 5.8 (m, 2, J = Hz, fine splitting, CHN), 5.0 (m, 2, CH=CH), 2–3.5 (m, 7), and 1.7 ppm (m, 1, J = 2 Hz, fine splitting C_7 H). *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.65; H, 6.00; N, 13.36.

Dicyclopentadiene Nitroxime (V and Va).—A suspension of 20 g of recrystallized dicyclopentadiene pseudonitrosite in 250 ml of dioxane was refluxed several hours under nitrogen. The pseudonitrosite dissolved to form a blue solution which became yellow on completion of the isomerization. Removal of the solvent by evaporation and trituration with ether afforded a solid which was filtered and washed with 1:1 ether–pentane. The crude nitroxime (18 g, 90% yield) of recrystallization from methylene chloride–pentane gave pale yellow crystals, mp 129–132°. Recrystallization from methanol favored one particular isomer. Crystals with mp 171° were obtained: nmr (d_6-acetone) δ 5.7 (s, 2, CH=CH), 4.8 (d, 1, J = 2 Hz, *endo*-$CHNO_2$) 2–3.5 (m, 8) and 1.7 ppm (m, 1, J = 2 Hz, fine splitting, C_7 H; ir ($CHCl_3$), 3600 (OH), 1800 (C=N), and 1560 cm^{-1} (NO_2). *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.48; H, 5.78; N, 13.74.

Norbornene *vs.* Cyclopentene.—The reaction of a mixture of 0.1 mol of norbornene and 0.1 mol of cyclopentene in 50 ml of ether with a 2:1 NO–air stream at 0° was followed by withdrawing samples of the reaction mixture at 25-min intervals and examining them on an Aerograph 1520B gas chromatogram with a DC-200 column at 100°. The ratios of norbornene/cyclopentene tabulated below indicate that norbornene was consumed at a much higher rate than cyclopentene.

Time, min	0	25	50	80	105
Ratio of norbornene/cyclopentene	1.0	0.95	0.75	0.3	0.05

After 1.75 hr the mixture was filtered; the product was washed with ether to give 5.2 g of product, mp 94–98°. A 1:1 mixture of the product with cyclopentene–pseudonitrosite[2c] showed a depressed melting point (88–91°); a similar mixture melting study with pure norbornene–pseudonitrosite revealed no depression. The infrared spectrum of the product was identical with that of the norbornene derivative[4] and different from the spectrum of cyclopentene–pseudonitrosite.

1,2-Dihydro-9-hydroximino-10-hydroxylaminodicyclopentadiene (VI).—A solution of 20.8 g (0.1 mol) of dicyclopentadiene nitroxime in 600 ml of absolute ethanol along with 1 g of 5% Pd-on-carbon catalyst was hydrogenated on a Parr apparatus, consuming 0.3 mol of H_2 after 8 hr. The catalyst was filtered and the solvent was evaporated to afford essentially quantitative yield (19 g) of hydroxylamino oxime (VI). Recrystallization from 95% ethanol afforded white crystals: mp 163°; nmr (CD_3OD) δ 4.5 (s, 3, exchanged with D_2O), 3.2 (d, 2, J = 2 Hz, *endo*-$C_{10}HN$), and 1–3 ppm (m, 12). *Anal.* Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.46; H, 7.99; N, 14.34.

4-Vinylcyclohexene-1 Nitroxime (VII).—A stirred solution of 108 g (1 mol) of 4-vinylcyclohexene-1 dissolved in 600 ml of a 1:1 mixture of ether–pentane at −10° was treated with a mixed stream of 10:1 nitric oxide–air until brown nitrogen dioxide gas was observed above the surface of the reaction mixture. The precipitate was filtered, washed with ether, and dried to give 19.4 g (11% yield) of a mixture of pseudonitrosite and nitroxime. The crude product was refluxed 1 hr in dioxane solution under nitrogen and evaporated. The crude nitroxime was triturated with ether, filtered, and recrystallized from methylene chloride–pentane to obtain crystals: mp 121°; ir ($CHCl_3$) 3600 (OH), 1800 (C=N), and 1560 cm^{-1} (NO_2); nmr (d_6-acetone) δ 5.2 (s, 2, CH=CH), 4.8 (s, 2, CH_2NO_2), 1.6 ppm (m, 7), and one exchangeable proton signal whose chemical shift varies with concentration. *Anal.* Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.65; H, 6.65; N, 14.85.

Vinylcyclohexane Pseudonitrosite (VIII).—The pseudonitrosite of vinylcyclohexane, prepared in the manner as described for 4-vinylcyclohexene-1, was obtained in 8% yield: mp 151° from methylene chloride–pentane; ir ($CHCl_3$) 1560 cm^{-1} (NO_2) with no hydroxyl absorption; nmr ($CDCl_3$) δ 5.8 (m, 1, CHNO), 5.2 (q, 1, J = 15 Hz, J_{AC} = 11 Hz, CH_ANO_2), 4.5 (q, 1, J_{AB} = 15 Hz, J_{BC} = 3 Hz, CH_BNO_2), and 1–2 ppm (m, 11). *Anal.* Calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.61; H. 7.56; N, 15.08.

Competition Studies with Vinylcyclohexane, 4-Vinylcyclohexene-1, and Cyclohexene.—Ethereal solutions containing vinylcyclohexane and 4-vinylcyclohexene-1, vinylcyclohexane, and cyclohexene and 4-vinylcyclohexene-1 and cyclohexene, each 0.2 M with respect to each olefin, were treated with 2:1 nitric oxide–air mixture at −15°. The change in concentration of olefin was followed by vpc examination, using an SE-30 column, an Aerograph 1520 instrument, and cyclohexane as internal reference. Response factors were determined empirically from the initial untreated solutions. The introduction of nitrogen oxides was carried out at a slow rate, so that the concentrations of nitrogen oxides are assumed to be constant and the rate first order with respect to olefin. The ratio of rate constants were calculated by the formula

$$\frac{K_c}{K_v} = \frac{\log (C_0/C_t)}{\log (V_0/V_t)}$$

(10) (a) T. V. VanAuken and E. A. Rick, *Tetrahedron Lett.*, **22**, 2709 (1968); (b) G. N. Sauser and A. L. Logothetis, *J. Org. Chem.*, **33**, 2330 (1968).

where K_c = rate constant for cyclohexene, K_v = rate constant for vinylcyclohexane, C_0 = molarity of cyclohexene at t = 0, C_t = molarity of cyclohexene at t, V_0 = molarity of vinylcyclohexane at t = 0, V_t = molarity of vinylcyclohexane at t. On this basis cyclohexene was found to be consumed at a rate 2.9 ± 0.4 times as fast as vinylcyclohexane, and 1.4 ± 0.1 times as fast as 4-vinylcyclohexene-1. The latter was consumed at a rate 2.0 ± 0.2 times that of vinylcyclohexane.

1-Amino-2-cyclohexylethane (IX).—A solution of 25 g (0.135 mol) of nitroxime VII in 600 ml of absolute ethanol along with 2 g of Raney nickel was hydrogenated at 75° and 1500 psi for 3 days. The catalyst was filtered, solvent was evaporated, and residue was distilled providing 5 g (27% yield) of distillate boilng at 130–148° (0.5 mm), which was converted to a crystalline hydrochloride: mp 258° (from 95% ethanol); nmr (D_2O) δ 3.0 (t, 2, CH_2N) and 1–2 ppm (m, 13). *Anal.* Calcd for C_8H_8-NCl: C, 57.63; H, 10.80; N, 8.90; Cl, 22.52. Found: C, 58.58; H, 11.01; H, 8.56; Cl, 21.90. The same hydrochloride could be obtained from the reduction of vinylcyclohexane pseudonitrosite (VIII) with excess lithium aluminum hydride in ether.

Vinylcyclohexane Nitroxime (X).—Refluxing a solution of 4 g of vinylcyclohexane pseudonitrosite (VIII) in 50 ml of dioxane under nitrogen for 8 hr, followed by evaporation of solvent afforded a quantitative yield of the nitroxime X. Recrystallization from methylene chloride–pentane gave crystals: mp 133°; ir ($CHCl_3$ 3600 (OH), 1800 (C=N) and 1560 cm^{-1} (NO_2); nmr (d_6-acetone) δ 5.2 (s, 2, CH_2NO_2), 1–2 ppm (m, 11) and one-proton absorption with concentration dependent chemical shift. *Anal.* Calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.60; H, 7.63; N, 14.98.

1-Hydroxylamino-2-cyclohexyl-2-hydroximinoethane (XI).—A solution of either 9.3 g (0.05 mol) of nitroxime X or 9.2 g (0.05 mol) of nitroxime VII dissolved in 250 ml of absolute alcohol along with 1 g of 5% palladium-on-carbon catalyst was hydrogenated on a Parr apparatus at 1–2 atm and ambient temperature. Two equivalents of hydrogen were consumed with VIII and 3 equiv with VII. The catalyst was filtered, solvent was evaporated, and the product was triturated with ether to give 6 g (70%) of white crystals: mp 112° from methylene chloride–ether; ir 3600 (OH), 330 (broad, NH), and 1650 cm^{-1} (C=N); nmr ($CDCl_3$) δ 6.8 (m, 3, exchanged with D_2O), 3.8 (s, 2, $-CH_2N$), and 1–2 ppm (m, 11). *Anal.* Calcd for C_8H_{16}-N_2O_2: C, 55.79; H, 9.36; N, 16.27; mol wt, 172. Found: C, 55.79; H, 8.91; N, 16.25; mol wt, 153.

1-Cyclohexyl-1,2-diaminoethane (XII).—A solution of 6.0 g (0.035 mol) of hydroxylamino oxime XI dissolved in ether was added dropwise to a solution of 8 g of lithium aluminum hydride in 500 ml of anhydrous ether with stirring under a nitrogen stream at such rate as to maintain a gently reflux of ether. After 12 hr the reaction mixture was introduced dropwise to a stirred, icecooled suspension of 0.5 kg of sodium sulfate, 250 ml of distilled water, and 300 ml of ether under nitrogen. After the refluxing of ether ceased, the inorganic salt was filtered and washed with additional ether. The ethereal filtrate was dried (Na_2SO_4) and evaporated affording 3.7 g (74%) of colorless oil XII. Treatment with excess anhydrous hydrogen chloride in ether gave the crystalline dihydrochloride, mp 268° (from alcohol). The identical product was obtained by similar reduction of X with lithium aluminum hydride or by Raney nickel catalyzed hydrogenation of either X or XI in alcohol solution at 1500 psi and 75°: nmr (D_2O) δ 3.4 (m, 3, $-CH-CH_2N$) and 1–2 ppm (m, 11). *Anal.* Calcd for $C_8H_{20}N_2Cl_2$: C, 44.66; H, 9.37; N, 13.02; Cl, 32.88. Found: C, 45.20; H, 9.58; N, 12.64; Cl, 31.79.

1,5-Cyclooctadiene Nitroxime.—The pseudonitrosites of 1,5-cyclooctadiene (XIII) and cyclooctene, and cyclooctene nitroxime (XVII) were prepared according to Klamann, *et al.*[8] The following procedure proved successful to isomerize XIII to the corresponding nitroxime XIV. A mixture of 46 g (0.25 mol) of 1,5-cyclooctadiene pseudonitrosite (XIII) and 5 g of anhydrous zinc chloride dissolved in 1 l. of absolute ethanol was refluxed under nitrogen for 1 hr, cooled, treated with 2 l. of aqueous saturated ammonium chloride solution, and extracted with methylene chloride. The methylene chloride extract was diluted with an equal volume of ether, washed several times with ammonium chloride solution, dried over sodium sulfate, and evaporated to give an oil which on trituration with methylene chloride gave 33 g (70%) of white crystals: mp 138–140° (from 95% ethanol); ir ($CHCl_3$) 3550 (OH), 1790 (C=N), and 1550 cm^{-1} (NO_2); nmr (d_6-acetone) δ 5.7 (m, 2, CH=CH), 5.2 (m, 1, $CHNO_2$), 2.3 ppm (m, 8) and (s, 1, OH) of varying chemical shift. *Anal.* Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21; mol wt, 184.2. Found: C, 52.23; H, 6.38; N, 15.26; mol wt, 185.

5-Aminocyclooctene-1 (XV).—Finely powdered 1,5-cyclooctadiene pseudonitrosite (XIII) (18.4 g, 0.1 mol) was cautiously introduced to a stirred mixture of 600 ml of absolute ether and 15.1 g (0.4 mol) of lithium aluminum hydride under nitrogen nitrogen atmosphere at such rate as to maintain gentle reflux of ether. The reaction was stirred an additional 16 hr under nitrogen after introduction of the pseudonitrosite was complete. Excess hydride was decomposed by careful dropwise introduction of the mixture to a stirred slurry of 1 kg of sodium sulfate, 250 ml of water, and 200 ml of ether under nitrogen at such rate as to maintain mild reflux of ether. The ethereal layer was decanted and treated with hydrogen chloride to provide 6.8 g (42%) of crystalline hydrochloride: mp 218° (from ethanol–ether); nmr (D_2O) δ 5.8 (m, 2, CH=CH), 3.3 (m, 1, CHN) and 1–2.5 ppm (m, 10). *Anal.* Calcd for $C_8H_{16}NCl$: C, 59.43; H, 9.98; N, 8.67; Cl, 21.93. Found: C, 59.50; H, 9.85; N, 8.72; Cl, 21.77. Hydrogenation of an alcoholic solution of XV with 5% palladized carbon affords cyclooctylamine hydrochloride.

2-Hydroxylaminocyclooctanone Oxime (XVI).—A solution of 12.2 g (0.066 mol) of nitroxime XIV in 250 ml of absolute ethanol along with 0.5 g of 5% Pd–C catalyst was hydrogenated in a Parr apparatus at ambient temperature until 3 equiv of hydrogen (0.1 mol) was consumed. The catalyst was separated by filtration and the solvent was removed to give pink oil which on trituration with chloroform provided 7 g (65%) of white crystals, mp 148° (from 95% ethanol). The identical substance was obtained in comparable yield by similar reduction of nitroxime (XVII) using 2 equiv of hydrogen: ir (KBr) 3500–2500 (OH and NH) and 1640 cm^{-1} (C=N); nmr (d_6-DMSO) δ 3.3 (t, 1, CHN) and 1.12–2.5 ppm (m, 12). *Anal.* Calcd for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27; mol wt, 172. Found: C, 55.72; H, 9.54; N, 16.27; mol wt, 167.

1,2-Diaminocyclooctane (XVIII).—A solution of 5.0 g (0.029 mol) of hydroxylaminooxime XVI in 200 ml of absolute ethanol along with 1 g of Raney nickel was placed in a high-pressure reactor and charged with hydrogen at 1500 psi. Th mixture was agitated 72 hr at 75°. The catalyst was removed by filtration and the solvent was evaporated. Distillation of the residue afforded 2.1 g (50%) of colorless oil, bp 65–75° (0.1 mm) which was converted to a hygroscopic dihydrochloride: mp 215° (from ethanol); nmr (D_2O) δ 3.7 (m, 2, CHN) and 1.5–2.3 ppm (m, 12). *Anal.* Calcd for $C_8H_{20}N_2Cl_2$: C, 44.67; H, 9.37; N, 13.03; Cl, 32.88. Found: C, 45.19; H, 9.59; N, 12.88; Cl, 31.64.

Conversion to the dibenzamide with benzoyl chloride and 2 *N* NaOH solution afforded a white solid, mp 286–288° (from ethyl acetate) *Anal.* Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.72; H, 7.60; N, 7.82.

Formation of the diacetamide afforded crystals: mp 160–170°; sublimed at 140° (0.05 mm); nmr (D_2O) δ 3.5–4 (m, 2, CHN), 1.7 (s, 6, CH_3), and 1.5 ppm [m, 12, $(CH_2)_6$]. *Anal.* Calcd for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 10.54; N, 12.38. Found: C, 63.62; H, 10.23; N, 12.35.

3,5-Diaminonortricyclene (XXII and XXIII).—A solution of 9.2 g (0.1 mol) of freshly distilled norbornadiene in 500 ml of anhydrous ether was treated at −15° with a stream of 2:1 nitric oxide–air until the presence of brown nitrogen dioxide was observed above the surface of the reaction mixture. The light tan solid precipitate was filtered, washed with ether, and dried to give 13.4 g (81%) adduct, mp 117–121°; roughly 60–70% of the adduct consisted of saturated, presumably nortricyclene derivative, as indicated by nmr (d_6-acetone) δ 4–6 (m, 2.3) and 1.5–3 ppm (m, 5.3). *Anal.* Calcd for $C_7H_8N_2O_2$: C, 50.00; H, 4.80; N, 16.66, mol wt, 168.2. Found: C, 50.09; H, 4.76; N, 16.77; mol wt, 170. The substance was unstable affording resinous products when treated with hot solvents. Treatment of 10 g (0.06 mol) of the adduct with 300 ml of absolute ethanol, 1 g of Raney nickel, and hydrogen at 1500 psi and 75° for 24 hr afforded 8 g of oil on filtration and evaporation. Distillation gave 3 g (40%) of colorless oil, bp 75–85° (0.4 mm); vpc examination with a Carbowax 20M–KOH column at 150° showed two major components in a 3:2 ratio.

Conversion to the dihydrochloride provided white crystals: mp 300° (from 95% ethanol); nmr (D_2O) δ 3.85 (m, 0.67, *endo*-CHN), 3.6 (m, 1.33, *exo*-CHN), 2.5 (m, 1, C_4H), and 1.9 ppm (m, 5), corresponding to a 2:1 mixture of *trans–cis* isomers. *Anal.* Calcd for $C_7H_{14}N_2Cl_2$: C, 42.65; H, 7.16; N, 22; Cl, 35.99. Found: C, 42.61; H, 7.21; N, 14.06; Cl, 35.98.

Conversion to the dibenzamide gave crystals, mp 286° (from methylene chloride). *Anal.* Calcd for $C_{21}H_{16}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 76.15; H, 6.38; N, 8.15.

Conversion to the diacetamide with acetic anhydride and triethylamine in ether afforded white precipitate: mp 220–225°; nmr in accord with 70% *trans*–30% *cis* mixture. *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.47; H, 7.88; N, 13.34. Recrystallization from methanol afforded white crystals: mp 278–281°, the *cis-exo* isomer; nmr (2:1 D_2O–CD_3OD) δ 3.7 (m, 2, *endo*-CHN), 2.2 (m, 1, C_4-H), 2.0 (s, 6, CH_3), and 1.5 ppm (m, 5). Recrystallization of the second crop from methanol gave the *trans* isomer: mp 226–227°; nmr (D_2O) δ 4.0 (m, 1, *exo*-CHN), 3.7 (m, 1, *endo*-CHN), 2.1 (m, 1, C_4-H), 2.02 (s, 3, CH_3), 2.01 (s, 3, CH_3), and 1.5 ppm (m, 5).

Registry No.—Dinitrogen trioxide, 10544-73-7; IV, 24695-03-2; IVa, 24695-04-3; V, 24695-05-4; Va, 24695-06-5; VI, 24695-07-6; VII, 24711-06-6; VIII, 24711-07-7; IX, 4442-85-7; IX hydrochloride, 5471-55-6; X, 24711-10-2; XI, 24711-11-3; XII dihydrochloride, 24704-32-3; XIV, 24711-12-4; XV hydrochloride, 24711-13-5; XVI, 10573-58-7; XVIII, 24704-33-4; XVIII hydrochloride, 24704-34-5; XVIII dibenzamide, 24711-15-7; XVIII diacetamide, 24711-16-8; XXII, 24695-08-7; XXII dihydrochloride, 24694-51-7; XXII dibenzamide, 24695-10-1; XXII diacetamide, 24694-52-8; XXIII, 24694-09-8; XXIII dihydrochloride, 24694-53-9; XXIII dibenzamide, 24694-54-0; XXIII diacetamide, 24694-55-1.

Acknowledgment.—The author is indebted to Mr. J. J. Porcelli for experimental assistance.

1,2-Hydroxylamino Oximes and Pyrazine N,N-Dioxides

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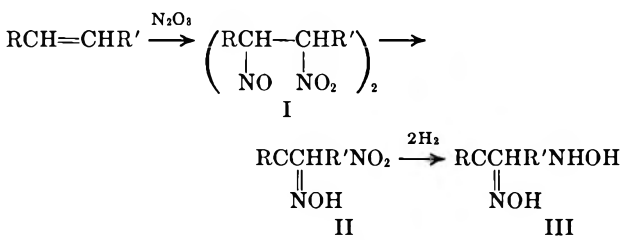
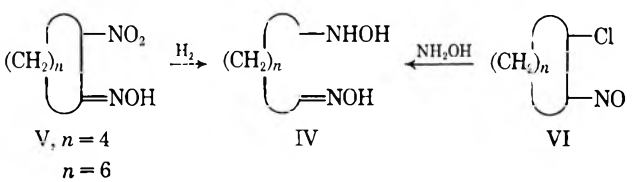
1,2-Nitroximes obtained from the isomerization of olefin–dinitrogen trioxide adducts are selectively reduced with palladized carbon to afford 1,2-hydroxylamino oximes. The latter class of compounds can be reduced to vicinal diamines, oxidized to 1,2-dioximes, form stable chelates with mercuric salts, and undergo a novel acid-catalyzed autocondensation to pyrazine N,N-dioxides.

The reaction of dinitrogen trioxide with olefins affords 1,2-nitronitroso dimers, commonly referred to as pseudonitrosites I.[2] These adducts can be converted to the more soluble isomers, the corresponding 1,2-nitroximes II.[2,3] The latter undergo a general, selective hydrogenation to 1,2-hydroxylamino oximes III in the presence of a palladized carbon catalyst. The derivatives are readily isolated as the acetic acid salts which can be smoothly converted back to free hydroxylamino oximes. Thus, the nitroxime derived from N_2O_3 addition to *cis*- or *trans*-butene-2 is converted to IIIa, and α-nitroacetophenone oxime (IIIb) derived from styrene is converted to IIIb in over 90% yield.



a, R = R = CH_3
b, R = C_6H_5; R = H
c, R = *c*-C_6H_{11}; R = H

Two equivalents of hydrogen are consumed to reduce the nitro group, and olefinic double bonds present in the nitroxime also undergo reduction. Thus, the same hydroxylamino oxime IVb (n = 6) is obtained from either the saturated nitroxime Vb, derived from cyclooctene, or the unsaturated derivative, 1,5-cyclooctadiene nitroxime, with the consumption of 2 or 3 mol of hydrogen, respectively. Similarly, IIIc can be obtained from either IIc or from the unsaturated nitroxime derived from 4-vinylcyclohexene-1.[3] The cyclohexene derivative IVa (n = 4) is identical with that prepared from the reaction of hydroxylamine with the nitrosyl chloride adduct of cyclohexene VIa (n = 4).[4] Owing to the mechanistic differences in orientation between nitrosyl chloride and dinitrogen trioxide additions to olefins, different hydroxylamino oximes would be expected, starting with unsymmetrical olefins from the two synthetic approaches.



The 1,2-hydroxylamino oxime derivatives possess a pair of vicinal carbon–nitrogen bonds which can be reduced to diamines. Either lithium aluminum hydride or Raney nickel catalyzed hydrogenation converts IVb to the corresponding *vic*-diamine, namely 1,2-diaminocyclooctane. The hydroxylamino group is susceptible to oxidation, and in the case of the styrene derivative IIIb, treatment with ferric chloride affords the 1,2-dioxime of phenylglyoxal. Similarly, the butene-2 derivative VIIa is converted to dimethylglyoxime, but in other cases oxidation by ferric chloride pro-

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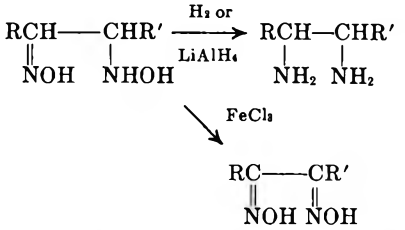
(2) (a) H. Wieland, *Justus Liebigs Ann. Chem.*, **424**, 71 (1920); *Ber.*, **36**, 2558 (1903). (b) D. Klamann, W. Koser, P. Weyerstahl, and M. Fligge, *Chem. Ber.*, **98**, 1831 (1965). (c) M. L. Scheinbaum, *Amer. Chem. Soc. Div. Petrol. Chem., Prepr.*, **13**, 193 (1968).

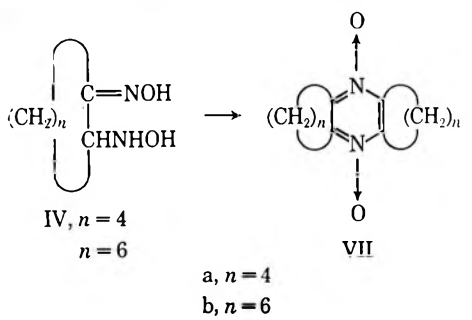
(3) M. L. Scheinbaum, *J. Org. Chem.*, **35**, 2785 (1970).

(4) L. B. Volodarskii and Yu. G. Putsykin, *J. Org. Chem. USSR*, **3**, 1642 (1967).

ceeds further, sometimes regenerating the nitroxime. Reaction of IIIb with mercuric chloride affords a stable 2:1 chelate.



Acid-catalyzed condensation with carbonyl compounds has been reported to result in the formation of imidazole oxide derivatives.[5] A related acid-catalyzed autocondensation occurs when hydroxylamino oximes are treated with concentrated sulfuric acid. The reaction may involve elimination of hydroxylamine along with accompanying oxidation. The major product is the pyrazine N,N-dioxide derivative. Thus, the cyclohexene derivative IVa affords octahydrophenazine N,N-dioxide (VIIa, $n = 4$) in 30% yield. The nmr of VIIa contains multiplets of equal area at δ 2.9 ($CH_2C{=}$) and 1.9 ppm ($CH_2CH_2C{=}$). Reaction of the N,N-dioxide with selenium affords phenazine in poor yield. In like manner, IVb is converted to the corresponding pyrazine N,N-dioxide (VIIb, $n = 6$) in 50% yield on treatment with sulfuric acid. The nmr spectrum of VIIb has three equal area multiplets at δ 2.9 ($CH_2C{=}$), 1.9 ($CH_2CH_2C{=}$), and 1.5 ppm ($CH_2CH_2CH_2C{=}$).



Experimental Section

Infrared spectra were taken on a Beckman IR-5, nmr spectra with a Varian A-60, using TMS as internal reference. Melting points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories.

Dinitrogen Trioxide Adducts.—Adducts of olefins and N_2O_3 were obtained by treating ethereal solutions of olefin at −20 to 0° with a 2:1 stream of nitric oxide–air until unabsorbed, brown nitrogen dioxide gas was observed at the surface of the reaction mixture. Pseudonitrosites of the following olefins were obtained: butene-2 (29%),[2b] vinylcyclohexane (8%),[2c] 4-vinylcyclohexene-1 (11%),[2c] styrene (60%),[1c] cyclohexene (47%),[2b] cyclooctene (27%),[2b] and 1,5-cyclooctadiene (83%).[2b]

Preparation of Nitroximes.—A mixture of 0.25 mol of olefin–dinitrogen trioxide adduct, 5.0 g anhydrous zinc chloride, and 1 l. of absolute ethanol or methanol was refluxed under nitrogen. The adduct dissolved to form a blue solution which changed to green and finally yellow as the nitroso monomer was converted to nitroxime. Completion of the isomerization required about an hour and was indicated by disappearance of the green color. The mixture was cooled, treated with 2 l. of saturated aqueous ammonium chloride solution and extracted several times with methylene chloride. The extracts were washed with saturated sodium chloride solution, dried (sodium sulfate), and evaporated to give high yields of nitroximes.

(5) L. B. Volodarskii and G. A. Kutikova, *Tetrahedron Lett.*, No. 9, 1065 (1968).

3-Nitrobutan-2-one oxime (IIa), an oil, identical in properties with that described by Klamann, *et al.*,[2b] nmr (in CCl_4) δ 5.2 (q, 1, $CHNO_2$), 1.9 (5,3, CH_3), and 1.8 ppm (d, 3, CH_3), was obtained (over 90%) from the pseudonitrosite of *cis*- or *trans*-butene-2. α-Nitroacetophenone oxime[1a] (IIb), mp 91° (from ether–hexane), nmr ($CDCl_3$) δ 7.5 (m, 5, C_6H_5) and 5.7 ppm (s, 2, CH_2), was obtained in over 90% yield from styrene pseudonitrosite. 2-Nitrocyclohexanone oxime (IVa), oil, was obtained from cyclohexene pseudonitrosite. Conversion to the 2,4-dinitrophenylhydrazone of 2-nitrocyclohexanone, mp 154°, occurred in over 90% yield. Calcd for $C_{12}H_{13}N_5O_6$: C, 44.71; H, 4.07; N, 21.71. Found: C, 44.60; H, 4.28; N, 21.01. The nitroximes obtained exhibited the following ir bands ($CHCl_3$): 3550 (OH), ~1790 (C=N), and 1550 cm^{-1} (NO_2).

Preparation of Hydroxylamino Oximes.—A solution of 0.05 mol of nitroxime in 250 ml of absolute ethanol along with 0.5 g of 5% palladium on carbon catalyst was hydrogenated in a Parr apparatus at ambient temperature until 0.1 mol of hydrogen was consumed. The catalyst was filtered and the solvent was evaporated to afford crude hydroxylamino oximes which could either be crystallized directly by trituration with methylene chloride or treated with acetic acid and ether to give the crystalline acetic acid salts, which could be readily regenerated to the free hydroxylamino oximes. The following derivatives were obtained.

3-Hydroxylaminobutan-2-one oxime (IIIa) was obtained from IIa in 90% yield: mp 78° (from methylene chloride–ether); ir ($CHCl_3$) 3600 (OH) and 3300 cm^{-1} (NH); nmr (CD_3OD) δ 3.3 (q, 1, CHN), 1.6 (s, 3, CH_3), and 0.9 ppm (d, J = 7 Hz, 3, CH_3). *Anal.* Calcd for $C_4H_{10}N_2O_2$: C, 40.66; H, 8.53; N, 23.71; mol wt 118. Found: C, 40.50; H, 8.54; N, 23.95 mol wt 119.

α-Hydroxylaminoacetophenone oxime (IIIb) was obtained from IIb in 90% yield: mp 128° (from 95% alcohol); nmr (CD_3OD) δ 7.5 (m, j, C_6H_5) and 4.1 ppm (s, 2, CH_2). *Anal.* Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.98; H, 6.11; N, 16.82.

2-Hydroxylaminocyclohexanone oxime (IVa) from Va in 90% yield, mp 100° (from 95% ethanol), was identical in properties with a sample prepared by the method of Volodarskii and Putsykin.[4] *Anal.* Calcd for $C_6H_{12}N_2O_2$: C, 49.98; H, 9.39; N, 19.43; mol wt 144. Found: C, 49.85; H, 8.25; N, 19.32; mol wt, 147. The preparations of IVb and IIIc have previously been described.[2]

Ferric Chloride Oxidation.—A solution of 0.01 mol (1.66 g) of α-hydroxylaminoacetophenone oxime (IIIb) and 0.01 mol (2.71 g) of $FeCl_3 \cdot 6H_2O$ in 100 ml of ethanol was filtered and evaporated to give a dark oil which was dissolved in 1:1 methylene chloride–ether, washed with saturated aqueous ammonium chloride solution, dried (Na_2SO_4), and evaporated to give 0.4 g (25% yield) of the dioxime of phenylglyoxal: mp 147° (from ether–hexane); nmr (CD_3CN) δ 8.2 (s, 1, CH=N) and 7.2 ppm (m, 5, C_6H_5). *Anal.* Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07; mol wt, 164. Found: C, 58.48; H, 4.65; N, 16.73; mol wt, 170.

In the same manner 3-hydroxylaminobutan-2-one oxime (IIIa) was converted to dimethylglyoxime in 42% yield: mp 243° (from hexane); nmr (d_6-acetone) δ 1.4 ppm (s, CH_3). *Anal.* Calcd for $C_4H_8N_2O_2$: C, 41.37; H, 6.94; N, 24.13. Found: C, 41.83; H, 7.14; N, 23.75.

Preparation of the $HgCl_2$ Complex of VIIb ($(C_8H_{10}N_2O_2)_2 \cdot HgCl_2$.—A mixture of 1.66 g (0.01 mol) of α-hydroxylaminoacetophenone oxime (IIIb), 2.72 g (0.01 mol) of mercuric chloride, and 100 ml of absolute ethanol was stirred under nitrogen at ambient temperature for 12 hr and evaporated to give a purple-tinged solid which on extraction and crystallization from ether–pentane afforded 0.7 g (23%) of white crystals: mp 192°; nmr (CD_3CN–D_2O) δ 7.6–7.1 (m, 5, C_6H_5) and 4.6 ppm (s, 2, CH_2). *Anal.* Calcd for $C_{16}H_{20}N_4O_4HgCl_2$: C, 31.82; H, 3.33; N, 9.28; Cl, 11.74; Hg, 33.22. Found: C, 31.68; H, 3.26; N, 9.18; Cl, 11.28; Hg, 29.

Preparation of Pyrazine N,N-Dioxides.—A finely powdered sample of 15 g (0.075 mol) of the acetic acid salt of 2-hydroxylaminocyclohexanone oxime (IVa) was introduced in small portions at a time to 10 ml of concentrated sulfuric acid (sp gr 1.84) at 0° with mechanical stirring. The slurry was gradually warmed to ambient temperature and allowed to stir for 24 hr. The crude reaction mixture was poured into ice, made basic with 2 *N* NaOH solution to pH 8–9, and extracted several times with ethyl acetate at 0°. The extracts were washed with

saturated NaCl solution, dried (Na_2SO_4), and evaporated to give 4.9 g of yellow oil which on trituration with ether gave pale yellow crystals of octahydrophenazine N,N-dioxide (VIIa) (30% yield). Recrystallization from methylene chloride–pentane afforded white crystals: mp 230°; ir ($CHCl_3$), 3000, 1720 (w), 1580 (w), 1470, 1360, 1340, and 1100 cm^{-1} (s); nmr ($CDCl_3$) δ 2.9 (m, 8, $CH_2C=$) and 1.9 ppm (m, 8, CH_2). *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72; mol wt, 220. Found: C, 64.76; H, 7.13; N, 12.70; mol wt, 250.

In like manner, VIIb was prepared in 50% yield from 2-hydroxylaminocyclooctane oxime (IVb).[2] White crystals, mp 248° (from methylene chloride–pentane), were obtained: ir ($CHCl_3$) 3000, 1730 (w), 1610 (w), 1460, 1340 (s), 1290, and 1100 cm^{-1} (s); nmr ($CDCl_3$) δ 3.2 (m, 8, $CH_2C=C$), 1.9 (m, 8, CH_2), and 1.5 ppm (m, 8, CH_2). *Anal.* Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14; mol wt, 276. Found: C, 69.67; H, 8.83; N, 10.04; mol wt, 295.

Treatment of VIIa (0.5 g) with 0.5 g of selenium at 350° under nitrogen for several hours gave a condensate which on extraction with methylene chloride and evaporation provided 50 mg of orange oil. Vacuum distillation of this residue in a Kugelrohr tube afforded 5 mg of sublimate which was identical in mixture melting point and vpc properties with phenazine.

Registry No.—IIa, 2567-33-1; IIb, 21205-24-3; IIIa, 24707-22-0; IIIb, 24707-24-2; IVa, 13757-09-0; VIIa, 24716-05-0; VIIb, 24716-06-1; 2-nitrocyclohexanone (2,4-dinitrophenylhydrazone), 10269-95-1; phenylglyoxal (dioxime), 4589-97-3; dimethylglyoxime, 95-45-4.

Acknowledgment.—The author is indebted to Mr. J. J. Porcelli for experimental assistance.

Aromatic N-Oxides. VI. Anhydro Base Intermediate and the Rate-Controlling Step in the Reaction of 4-Alkylpyridine N-Oxide with Acid Anhydrides[1]

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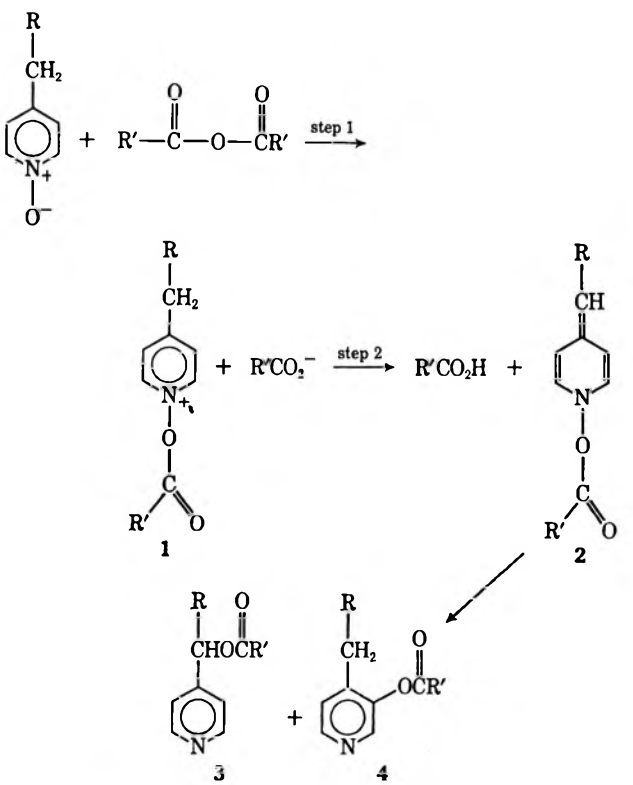
Evidence for the first step of the reaction of 4-alkylpyridine N-oxides with acid anhydrides was obtained by isolation of 1-acetoxy-4-methylpyridinium and 1-acetoxy-4-benzylpyridinium perchlorates and their conversion by triethylamine in acetonitrile to the corresponding rearranged esters. The reaction of 1-acetoxy-4-benzylpyridinium perchlorate (1) and triethylamine was also examined spectroscopically and provided uv evidence for the intermediate anhydro base, 1-acetoxy-4-benzal-1,4-dihydropyridine (2), whose absorption spectrum resembled 1-methyl-4-benzal-1,4-dihydropyridine. The absence of deuterium exchange in the reaction of 1-acetoxy-4-(α,α-dideuteriobenzyl)pyridinium perchlorate with sodium acetate in acetic acid–acetonitrile and the dependence of the conversion of 1 to 2 on base strength support the assignment of this step as rate controlling.

The generally accepted mechanism for the reaction of 4-alkylpyridine N-oxides and acid anhydrides has been reviewed in several places.[1,3] In this report we offer evidence in support of the formation of the 1-acyloxy-4-alkylpyridinium cation (1) in step 1, of the anhydro-base intermediate (2), and of the rate-controlling step 2.

The isolation of cation 1 was accomplished as the perchlorate salt from the reaction of 4-methyl- and 4-benzylpyridine N-oxides and acetic anhydride in the presence of perchloric acid. Structural assignments for these salts were based on elemental analysis, a characteristic carbonyl frequency (1825–1830 cm^{-1}),[4,5] and the reaction of these salts with triethylamine in acetonitrile to produce the esters: 4-pyridylmethyl acetate (3, R = H, R′ = CH_3) and 3-acetoxy-4-methylpyridine (4, R = H, R′ = CH_3) (both esters identified spectroscopically) from 1-acetoxy-4-methylpyridinium (1, R = H, R′ = CH_3) perchlorate, and phenyl-4-pyridylmethyl acetate (3, R = C_6H_5, R′ = CH_3) from 1-acetoxy-4-benzylpyridinium (1, R = C_6H_5, R′ = CH_3) perchlorate. Identification of phenyl-4-pyridylmethyl acetate was achieved by comparison with an authentic sample, saponification of the ester to the known phenyl-4-pyridylmethanol,[6] and isolation of the



ester from the reaction of 4-benzylpyridine N-oxide and acetic anhydride. These conversions of the perchlorate salts of 1 by triethylamine in acetonitrile to the same esters as obtained from the corresponding 4-alkylpy-

(1) For paper V in this series see V. J. Traynelis and Sr. A. I. Gallagher, *J. Amer. Chem. Soc.*, **87**, 5710 (1965).

(2) (a) Department of Chemistry, West Virginia University, Morgantown, W. Va. (b) Abstracted from the Ph.D. dissertation of A. I. G.,

(3) V. J. Traynelis in "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Interscience Publishers, New York, N. Y., 1969, pp 31–37.

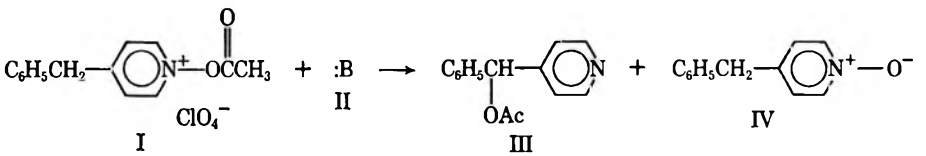
(4) C. W. Muth and R. S. Darlak, *J. Org. Chem.*, **30**, 1909 (1965).

(5) V. J. Traynelis and P. L. Pacini, *J. Amer. Chem. Soc.*, **86**, 4917 (1964).

(6) A. E. Tschitschibabin, *Chem. Ber.*, **37**, 1371 (1904).

TABLE I

REACTION OF 1-ACETOXY-4-BENZYLPYRIDINIUM PERCHLORATE AND BASE



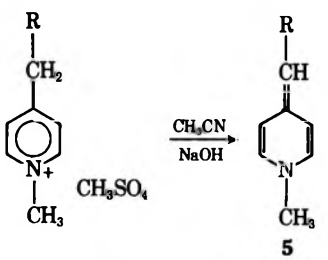
I, mol	CH_3CN, ml	Base	II, mol	CH_3CN, ml	Time	Temp, °C	Procedure	% yield II	% yield IV
0.012[a]	100	Et_3N	0.012[a]	100	1 hr	0	A	60	
0.018	75	Et_3N	0.018	25	<5 min[b]	0	B	26	
					25 min[b,c]	0	B	40	
0.012	37		0.012	5	2.25 hr[d]	0	B	54	
0.012[e]	20	NaOAc	0.012[e]	10	15 min	87	C	0	93
0.014[f]	25	NaOAc	0.014[f]	13	1 hr	87	D	32	24
0.012[e]	20	NaOAc	0.012[e]	10	1.33 hr	87	D	38	
0.017[g]	25	NaOAc	0.017[g]	10	3 hr	87	D	50	6

[a] Reactants were precooled to 0° and added simultaneously to the reaction flask. [b] Data taken from one reaction, one-half was processed immediately after addition (<5 min), the other half after 25 min. [c] This reaction was followed by ir and visible spectroscopy and is reported in the Experimental Section. [d] Progress of the reaction was followed by ir; the 1-acetoxy carbonyl at 1825 cm^{-1} slowly disappeared while the ester carbonyl at 1739 cm^{-1} appeared and increased. The reaction was quenched when the 1825 cm^{-1} absorption was absent. [e] Acetic acid (10 ml) was added to the 1-acetoxy salt while sodium acetate was dissolved in 14 ml of acetic acid. [f] Same as *e* except the acetic acid volumes were 13 and 15 ml, respectively. [g] Same as *e* except the acetic acid volumes were 10 and 25 ml.

ridine N-oxide acetic anhydride reaction led to the conclusions that cation **1** is a reasonable intermediate in this reaction and that rearrangement to ester products requires the action of base on **1**.

A spectral study of the reaction of 1-acetoxy-4-benzylpyridinium perchlorate and triethylamine in acetonitrile provided information regarding the intermediacy of the anhydro base **2**. The model system used which corresponded to **2** was the known 1-methyl-4-benzal-1,4-dihydropyridine (**5**, R = C_6H_5), prepared *in situ* by the reaction of 1-methyl-4-benzylpyridinium methosulfate in acetonitrile and aqueous NaOH.

The uv-visible spectrum of **5**, R = C_6H_5, in CH_3CN–H_2O, 90:10 (v/v), showed an absorption maximum at 370 mμ (357 mμ in anhydrous CH_3CN) which reached



5

maximum intensity in 2 hr (ε 18,900 assuming complete conversion of salt to anhydro base **5** in 2 hr). and then began to decay. When a precooled solution of equimolar amounts of 1-acetoxy-4-benzylpyridinium perchlorate in CH_3CN and triethylamine in CH_3CN were mixed at 0°, a band appeared rapidly at 352 mμ (absorbance 0.780) and remained constant for at least 10 min (absorbance 0.775) but by 25 min had decreased markedly (absorbance 0.145). If one assumes that the molar extinction coefficient for 1-acetoxy-4-benzal-1,4-dihydropyridine (**2**, R = C_6H_5, R′ = CH_3) is comparable to that of 1-methyl-4-benzal-1,4-dihydropyridine and that these solutions obey Beer's Law, the concentration of the acetoxy anhydro base (**2**, R = C_6H_5, R′ = CH_3) in the first two aliquots would be approximately 4×10^{-4} molar. This concentration of anhydro base compared to the concentration of reactants (0.18 *M*) reflects a 0.2% conversion to the intermediate anhydro base **2**. Thus the low conversion to anhydro base along with the constant concentration is suggestive of a steady-state situation. Aliquots also taken upon mixing, after 10 and 25 min were subjected to infrared spectral measurements and showed that the first spectrum after mixing had a more intense band for $>C-OOCCH_3$ (1739 cm^{-1}) than $>N^+-OOCCH_3$ (1825 cm^{-1}). Spectra taken after 10 and 25 min showed continued increase in intensity of the 1739-cm^{-1} band with a concurrent decrease in the 1825-cm^{-1} band. The infrared spectra clearly demonstrate the rapid conversion of the cation **1** (R = C_6H_5, R′ = CH_3) to phenyl-4-pyridylmethyl acetate, while the appearance of a chromophore with λ_{max} 352 mμ upon mixing the reactants and eventual disappearance of this band supports an anhydro base **2** for the intermediate leading to ester products. Additional evidence in support of the anhydro base intermediate has been reported recently by Oae[7] employing the lepidine N-oxide benzoyl chloride reaction and deuterium labeling; however, the major products in this reaction had the benzoate in the C-3 position rather than attached to the side-chain methyl group.

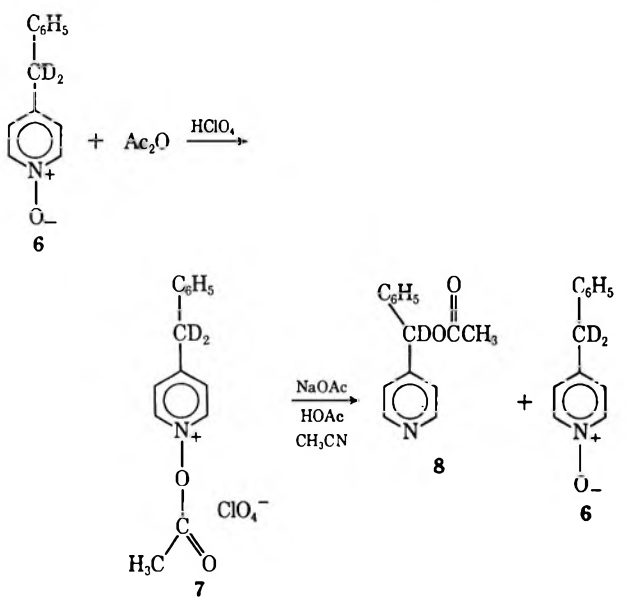
Application of the above approach to detect the presence of anhydro base in the reaction of 1-acetoxy-4-methylpyridinium perchlorate and triethylamine was unsuccessful. The reaction of 1,4-dimethylpyridinium methosulfate and base slowly produced an absorption maximum at 310 mμ which slowly disappeared; however, the reaction of 1-acetoxy-4-methylpyridinium perchlorate and triethylamine showed no absorption in the 310-mμ region but revealed the disappearance of the band at λ_{max} 254 mμ (N-acetoxy cation) and the appearance of absorption maxima at 276 and 265 mμ cor-

(7) S. Oae, S. Tamagaki, and S. Kozuka, *Tetrahedron Lett.*, 1513 (1966).

responding to a mixture of 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine.

A study of the reaction of 1-acetoxy-4-benzylpyridinium perchlorate with a variety of bases is summarized in Table I. These results show the need for base to promote the conversion of cation **1** to ester products *via* anhydro base **2**. In the reactions performed with sodium acetate in acetonitrile–acetic acid the nature of the reactants is less certain since the cation **1** (R = C_6H_5) can react with acetate ion to generate acetic anhydride and 4-benzylpyridine N-oxide. These conditions thus represent the standard N-oxide acetic anhydride reactants in acetonitrile–acetic acid solution with sodium perchlorate.

Oae and coworkers[8] have previously presented support for step 2 as rate determining by their deuterium kinetic isotope effect study which gave a value of K_H/K_D = 4.6 at 30° for the reaction of 4-picoline N-oxide and acetic anhydride. Additional support for step 2 as rate controlling was obtained from deuterium exchange studies similar to those reported for the 2-benzylpyridine N-oxide system.[5] 4-(α,α-Dideuteriobenzyl)pyridine N-oxide (**6**) was prepared by an exchange reaction of 4-benzylpyridine N-oxide in deuterium oxide catalyzed by triethylamine. The replacement of the two α,α-benzyl hydrogens by deuterium was complete (Calcd: 18.18 atom % excess deuterium. Found: 21.00%) and the nmr spectrum showed the absence of proton resonance in the region of the benzyl hydrogens. The excess deuterium incorporated into the molecule involves the partial exchange with the α-hydrogens of the pyridine ring.[9] The deuterated N-oxide **6** was converted to 1-acetoxy-4-(α,α-dideuteriobenzyl)pyridinium perchlorate (**7**). When **7** was



treated with sodium acetate in the presence of acetic acid and acetonitrile under conditions which led to approximately 50% reaction (see Table I, entry 5, for conditions and results with undeuterated compounds), no deuterium loss was found in the rearranged ester **8** (Calcd: 7.69 atom % excess deuterium. Found: 9.05%) and the N-oxide **6** (Found: 21.80 atom % excess deuterium) formed from **7** by hydrolysis. Also the nmr spectrum of ester **8** showed no absorption in the region of the benzylic proton.

The absence of deuterium exchange in the above experiments requires that the rate of conversion of anhydrobase **2** to products **3** and **4** is more rapid than the protonation of **2** to regenerate the cation **1**. The rapid conversion of **1** (R = C_6H_5, R′ = CH_3) by triethylamine to ester **3** (R = C_6H_5, R′ = CH_3) and the low concentration of anhydrobase **2** (R = C_6H_5, R′ = CH_3) (what appears to be a steady-state concentration) generated in this reaction both point to a more rapid disappearance of **2** in contrast to its formation from **1**. These exchange experiments are consistent with the assignment of step 2 as rate controlling and thus lend further support to this mechanism.

The above spectral observation of the anhydrobase **2** intermediate in the 4-alkylpyridine N-oxide system is in contrast to similar attempts to detect the anhydrobase in the 2-alkylpyridine studies. This may be rationalized by considering that the rearrangement reaction in the 4 system appears to be slower than in the 2-system. Thus the generation of anhydro base **2** reaches a concentration limit that permits its observation. The remaining question in the 4-alkylpyridine N-oxide system is the nature of the rearrangement of anhydrobase **2** to ester products **3** and **4**. This will be discussed in the subsequent paper.

Experimental Section[10]

4-Benzylpyridine N-oxide [mp 104–105° (lit.[11] mp 151°); nmr ($CDCl_3$) τ 6.03 (s, 2, $-CH_2C_6H_5$), 2.98 (d, J = 7.4 Hz, partially hidden under the phenyl multiplet, β-hydrogens on pyridine ring), 2.76 (sharp peak of multiplet, phenyl hydrogens, total intensity of 2.98 and 2.76 peaks is 7), 1.95 (d, 2, J = 7.4 Hz, α-hydrogens in pyridine); uv max (CH_3CN) 281 mμ (ϵ 18,900)] was prepared by oxidation of 4-benzylpyridine[12] by the procedure of Hands and Katritzky.[11]

Phenyl-4-pyridylmethyl Acetate.—A solution of 1.9 g (0.01 mol) of phenyl-4-pyridylmethanol, mp 125° (lit.[6] mp 126°), prepared by a photochemical reduction of 4-benzylpyridine in alkaline isopropyl alcohol, and 1.53 g (0.015 mol) of acetic anhydride was heated for 2 hr. After the acetic acid and excess acetic anhydride were removed *in vacuo*, distillation of the residue gave 1.7 g (75%) of phenyl-4-pyridylmethyl acetate: bp 137–139° (0.75 mm); $n^{20}D$ 1.5617; nmr ($CDCl_3$) τ 7.94 (s, 3, $-OOCCH_3$), 3.18 (s, 1, C_6H_5CHOAc), 2.74 (m, 7, phenyl hydrogens and the β-hydrogens in pyridine), 1.55 (d, 2, α hydrogens in pyridine); uv max (CH_3CN) 256 mμ (ϵ 2410), 264 (sh).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76. Found: C, 73.97; H, 5.69.

A **picrate** which was extremely light sensitive was prepared and recrystallization from ethanol gave an analytical sample, mp 124–125°.

Anal. Calcd for $C_{20}H_{16}N_4O_9$: C, 52.64; H, 3.53. Found: C, 52.94; H, 3.94.

Reaction of 4-Benzylpyridine N-Oxide and Acetic Anhydride.—A solution of 4-benzylpyridine N-oxide (9.26 g, 0.05 mol) in acetic acid (25 ml) was added over a 2-hr period to refluxing acetic anhydride (10.5 g, 0.102 mol) under nitrogen. Distillation

(8) S. Oae, S. Tamagaki, T. Negoro, K. Ogino, and S. Kozuka, *Tetrahedron Lett.*, 917 (1968).

(9) Sr. A. I. Gallagher, I. H. M., B. A. Lalinsky, and C. M. Cuper, *J. Org. Chem.* **35**, 1175 (1970).

(10) The microanalysis were carried out by Midwest Microlab, Inc. Indianapolis, Ind., or Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., while the deuterium analysis were performed by J. Nemeth, Urbana, Ill. Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer, the uv-visible spectra were recorded on a Bausch and Lomb Spectronic 505 instrument and the nmr spectra were determined by D. Schifferl or W. E. Hunter with a Varian Associates 60 Mc high resolution nmr spectrometer Model V-4300B.

(11) A. R. Hands and A. R. Katritzky, *J. Chem. Soc.*, 1754 (1958).

(12) The authors wish to thank Dr. F. A. Cislak, Reilly Tar and Chemical Co., Indianapolis, Ind., for a generous gift of 4-benzylpyridine.

of the reaction mixture gave 8.44 g (75%) of phenyl-4-pyridylmethyl acetate, bp 164–166° (3.75 mm), $n^{20}D$ 1.5618. The infrared spectrum of the ester was identical with that of the authentic sample.

The ester was saponified with KOH in water and gave phenyl-4-pyridylmethanol (80% yield), mp 121–122°. A mixture melting point with an authentic sample was not depressed.

1,4-Dimethylpyridinium Methosulfate.—Dimethyl sulfate (6.8 g, 0.054 mol) in anhydrous ether (5 ml) was added slowly to a stirred solution of 4-methylpyridine (5.0 g, 0.054 mol) in anhydrous ether (5 ml). The initial white emulsion slowly solidified and gave 11.0 g (96%) of 1,4-dimethylpyridinium methosulfate as very hygroscopic white solid. Recrystallization from dry acetonitrile–ether gave an analytical sample: mp 66–69° (sealed tube); uv max (CH_3CN) 255 mμ (ε 4500), 260 and 262 (sh).

Anal. Calcd for $C_8H_{13}NO_4S$: C, 43.82; H, 5.98. Found: C, 43.56; H, 6.33.

1-Methyl-4-benzylpyridinium Methosulfate.—Using the above procedure 4-benzylpyridine (5.0 g., 0.03 mol) and dimethyl sulfate (3.7 g,. 0.03 mol) in 10 ml ether gave 7.8 g (90%) of 1-methyl-4-benzylpyridinium methosulfate as a clear oil which could not be induced to crystallize: uv max (CH_3CN) 254 mμ (ε 5450), 261 (sh).

1-Acetoxy-4-methylpyridinium perchlorate [mp 84–86° (sealed tube) (lit.[4] 84.5–86°); ir (CH_3CN) 1831 cm^{-1} ($\gtrless N^+$–$OOCCH_3$); uv max (CH_3CN) 254 mμ (ε 4800), 261, 275 (sh)] was prepared in 72% yield according to the procedure of Muth and Darlak.[4]

1-Acetoxy-4-benzylpyridinium Perchlorate.—The reaction of 4-benzylpyridine N-oxide (3.7 g, 0.02 mol) in acetic acid (10 ml) and acetic anhydride (25 ml) with perchloric acid (0.5 *M*, 40 ml) gave 5.7 g (87%) of 1-acetoxy-4-benzylpyridinium perchlorate: mp 136–141°; uv max (CH_3CN) 253 mμ (ε 6200), 275 mμ (sh); ir (Nujol mull) 1825 cm^{-1} ($\gtrless N^+$–$OOCCH_3$). An analytical sample, mp 140–141°, was obtained by recrystallization from CH_3CN–ether.

Anal. Calcd for $C_{14}H_{14}ClNO_6$: C, 51.31; H, 4.31. Found: C, 51.52; H, 4.55.

Reaction of Pyridinium Salts with Base, Spectral Study. A. 1-Methyl-4-benzylpyridinium Methosulfate.—A solution of 1-methyl-4-benzylpyridinium methosulfate (0.05 ml of 0.01 *M* soln in CH_3CN) and 1 ml of 10% NaOH was diluted to 10 ml with acetonitrile (5×10^{-5} *M* in 1-methyl-4-benzylpyridinium methosulfate) and the uv-visible spectrum observed over several hr. An absorption maximum appeared shortly at 370 mμ, reached a maximum intensity after 2 hr, then began to decay. Assuming complete conversion to 1-methyl-4-benzal-1,4-dihydropyridine in 2 hr, the molar extinction coefficient has the value ε 18,900 [lit.[13] $\lambda_{max}^{Et_2O}$ 350 mμ (ε 8900); λ_{max} 388 mμ (ε 7950)].

Addition of 10% NaOH to an aqueous solution of 1-methyl 4-benzylpyridinium methosulfate gave a red-brown oil[14] which was extracted into acetonitrile and showed an absorption maximum at 370 mμ. After removal of the solvent, the brown oil was dried, redissolved in acetonitrile and showed an absorption maximum at 357 mμ.

B. 1-Acetoxy-4-benzylpyridinium Perchlorate.—A solution of triethylamine (1.85 g, 0.0183 mol) in acetonitrile (25 ml) cooled to 0° was added rapidly to a stirred solution of 1-acetoxy-4-benzylpyridinium perchlorate (6.00 g, 0.0183 mol) in acetonitrile (75 ml) precooled to 0°. Aliquots were removed immediately upon mixing, 10 and 25 min after addition and the ir and uv-visible spectra recorded for each aliquot. The uv-visible spectra were measured on solutions prepared by diluting a 1-ml aliquot to 10 ml of solution with acetonitrile. The ir spectrum taken of the aliquot removed immediately upon mixing showed a sharp decrease in the N-acetoxy carbonyl band at 1825 cm^{-1} and the appearance of the ester product carbonyl band at 1739 cm^{-1}. After 25 min of reaction time the 1825-cm^{-1} band was very small. The uv-visible spectrum of the aliquot taken immediately upon mixing had an absorption maximum $\lambda_{max}^{CH_3CN}$ 352 mμ (absorbance 0.780) which showed no change in λ_{max} or absorbance value after 10 min (0.775) but after 25 min the λ_{max} had an absorbance of 0.145. Product isolation and identification will be reported in a later section.

C. 1,4-Dimethylpyridinium Methosulfate.—An aliquot (0.1 ml) from a 1.12×10^{-2} molar absolution of 1,4-dimethylpyridinium methosulfate in acetonitrile was mixed with 0.25 ml of 10% sodium hydroxide solution and diluted to 10 ml with acetonitrile to give a solution 1.12×10^{-4} *M* in 1,4-dimethylpyridinium methosulfate. The uv spectrum recorded immediately upon preparation of the above solution was identical with that of 1,4-dimethylpyridinium methosulfate in acetonitrile. After 0.5 hr a broad absorption began to appear at about 300 mμ and developed into an intense absorption maximum at 310 mμ. This band began to decrease with the appearance of other absorption bands at longer wavelengths. After 15 hr the 310-mμ band had essentially disappeared.

D. 1-Acetoxy-4-methylpyridinium Perchlorate.—A cold solution of 1-acetoxy-4-methylpyridinium perchlorate and triethylamine (1×10^{-4} *M* in each reactant) in acetonitrile was observed spectroscopically. The absorption band due to the salt (λ_{max} 254 mμ) slowly disappeared; however, no band appeared in the 310-mμ region. The final uv curve showed absorption maxima at 276 and 265 mμ which corresponded to a mixture of 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine. The ir of the reaction mixture had the carbonyl stretching frequency at 1739 cm^{-1}.

Reaction of 1-Acetoxy-4-benzylpyridinium Perchlorate with Base.—A solution of the base in acetonitrile was added rapidly to a solution of 1-acetoxy-4-benzylpyridinium perchlorate in acetonitrile and subjected to the conditions in Table I. The reaction mixture was processed by one of the following procedures. (a) The reaction mixture was concentrated, *in vacuo*, to one-half volume, diluted with water and extracted with ether. After the extract was dried and the solvent removed, the residue was identified as phenyl-4-pyridylmethyl acetate by comparison of its infrared spectrum with that of an authentic sample. The picrate, mp 121–122°, was prepared and a mixture melting point with an authentic sample was not depressed. (b) The reaction mixture was poured into water, extracted with chloroform, and the extract was washed with saturated sodium bicarbonate, dried and the solvent was removed. The residue was chromatographed on Florisil (25 g/g of residue). Elution with benzene–chloroform (90–10) gave phenyl-4-pyridylmethyl acetate while 4-benzylpyridine N-oxide was eluted with a chloroform–methanol (90–10) solution. The ester was identified as in method a and the recovered N-oxide identified by melting point and a mixture melting point with an authentic sample. (c) The reaction mixture was quenched in ice and basified with solid sodium bicarbonate. The alkaline solution was extracted with chloroform, the extract dried and solvent removed. The residue was identified as 4-benzylpyridine N-oxide. (d) Same procedure as in c except the aqueous layer was made strongly alkaline and the chloroform extract was processed as in (b).

Deuterium Label Experiments. 4-(α,α-Dideuteriobenzyl)-pyridine N-Oxide.—Using the procedure of Traynelis and Pacini[5] a 91% yield of recrystallized (ethyl acetate Skelly B) 4-(α,α-dideuteriobenzyl)pyridine, mp 105–107° (sealed tube), nmr ($CDCl_3$) τ 2.97 (d, J = 7.2 Hz) as part of a multiplet with a sharp peak at 2.78 (total intensity 7, β hydrogens of pyridine and phenyl hydrogens), 1.94 (d, 2, J = 7.2 Hz, α hydrogens in pyridine), was obtained. The region of the benzylic hydrogens τ 6.03 was completely blank.

Anal. Calcd for $C_{12}H_9D_2O$:[15] C, 76.97; H, 5.92; D, 18.18 atom % excess. Found: C, 76.41; H, 6.10; D, 21.00 atom % excess.

1-Acetoxy-4-(α,α-dideuteriobenzyl)pyridinium Perchlorate.—Employing the procedure described earlier, 6.3 g (89%) of 1-acetoxy-4-(α,α-dideuteriobenzyl)pyridinium perchlorate, mp 143–144°, was obtained from the reaction of 4-(α,α-dideuteriobenzyl)-pyridine N-oxide (4.00 g, 0.024 mol) in acetic acid (10 ml) and acetic anhydride (25 ml) with perchloric acid (48 ml, 0.5 *M*). The ir had a carbonyl absorption at 1825 cm^{-1}.

Reaction of 1-Acetoxy-4-(α,α-dideuteriobenzyl)pyridinium Perchlorate and Sodium Acetate in the Presence of Acetic Acid.—Sodium acetate (1.38 g, 0.017 mol) in acetic acid (25 ml) and acetonitrile (10 ml) was added rapidly to a stirred solution of 1-acetoxy-4-(α,α-dideuteriobenzyl)pyridinium perchlorate (5.50 g, 0.017 mol) and the mixture was refluxed 1 hr. The reaction was processed according to procedure B described for the undeuterated salt. Column chromatography gave upon elution

(13) L. C. Anderson and N. V. Seeger, *J. Amer. Chem. Soc.*, **71**, 343 (1949). The extinction coefficients listed above were estimated from the curve reported in the literature.

(14) H. Decker, *Chem. Ber.*, **38**, 2493 (1905).

(15) The % H was calculated using the formula weight of the deuterated molecule and the number of hydrogen atoms × 1.008 of the undeuterated molecule. The conversion factor for regular water was used for the combustion water collected in the absorption tube.

with benzene–chloroform (90–10) 0.99 g (26%) of phenyl-(4-pyridyl)-1-deuteriomethyl acetate: n^{20}D 1.5621; nmr ($CDCl_3$) τ 7.94 (s, 3, acetate methyl protons), a hint of a peak at 3.15 (benzylic proton), 2.82 (doublet) partially hidden under the multiplet with a sharp peak at 2.73 (total intensity 7, β protons in pyridine and phenyl protons), 1.47 (d, 2, α protons in pyridine).

Anal. Calcd for $C_{14}H_{12}DNO_2$:[15] C, 73.67; H, 5.74; D, 7.69 atom % excess. Found: C, 74.03; H, 5.85; N, 9.05 atom % excess.

Continued elution with chloroform–methanol (90–10) gave 0.80 g (25%) of 4-(α,α-dideuteriobenzyl)pyridine N-oxide: mp 103–105°; nmr ($CDCl_3$) identical with that of the authentic sample. A sample was recrystallized from ethyl acetate for analysis, mp 105–106°.

Anal. Calcd for $C_{12}H_9D_2NO$:[15] C, 76.97; H, 5.92; D, 18.18 atom % excess. Found: C, 76.58; H, 6.03; D, 21.80 atom % excess.

Registry No.—Phenyl-4-pyridylmethyl acetate, 24929-18-8; phenyl-4-pyridylmethyl acetate picrate, 24866-72-6; 1,4-dimethylpyridinium methosulfate, 24866-73-7; 1-acetoxy-4-benzylpyridinium perchlorate, 24866-74-8; 4-(α,α-dideuteriobenzyl)pyridine N-oxide, 24866-75-9; phenyl-(4-pyridyl)-1-deuteriomethyl acetate, 24866-76-0.

Photochemistry of Unsaturated Nitrogen Containing Compounds. VII. Photolysis of Phenylhydrazones[1]

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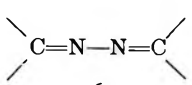
The photochemistry of benzaldehyde phenylhydrazone (1), benzophenone hydrazone (2), benzaldehyde diphenylhydrazone (3), benzophenone phenylhydrazone (4), and benzophenone diphenylhydrazone (5) has been investigated. The products formed from these irradiations indicate that hydrazones are capable of two types of reaction. First, the nitrogen–nitrogen bond of the hydrazone system may be cleaved in a process which results in the formation of an amine and an imine (isolated in most cases as the corresponding aldehyde or ketone). In cases where the hydrazone is derived from an aldehyde, this same reaction pathway also produces a nitrile. The second type of reaction, observed only for benzaldehyde phenylhydrazone (1) and benzophenone hydrazone (2), is one which reduces the hydrazone system to a hydrocarbon; hence, this latter reaction type is a photochemical analog of the Wolff–Kishner reduction Possible mechanisms for these two reaction processes are proposed and discussed.

As a part of a continuing study of the photochemistry of unsaturated systems containing nitrogen,[2] the light-induced reactions of a series of five hydrazones (**1–5**) have been investigated. Interest in these molecules was stimulated by recent findings arising from the photochemistry of a related group of compounds, the azines (**6**). Several studies during the past few years[3–5] have indicated that the photolysis of azines leads either to cleavage of the nitrogen–nitrogen bond in the azine system, the major reaction pathway, or complete loss of nitrogen from the molecule, a minor process. The structural similarity between the azine (**6**) and hydrazone (**7**) systems suggested a possible similarity in their photochemical reaction.



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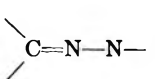

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Of the five compounds studied, only benzaldehyde phenylhydrazone (**1**) has been mentioned previously in the chemical literature as a reactant in light-initiated processes. In these earlier reports the interest in **1** centered around the observation that it is photochromic[6,7] and that it may undergo a photochemical *cis–trans* isomerization;[8] however, in no case was a general study of the photochemistry of this compound conducted. Thus, in order to establish and extend the knowledge of the photochemical reactions of hydrazones as well as to compare hydrazone (**7**) and azine (**6**) photochemistry, the following results from the photolyses of hydrazone systems **1–5** are reported.

Results

Vycor-filtered irradiation of a methanol solution of benzaldehyde phenylhydrazone (**1**) under nitrogen produced upon solvent removal a reddish-brown oil. Chromatography on Florisil separated the reaction mixture into five fractions, one of which was unreacted starting material. The other four were diphenylmethane (14%), benzonitrile (8%), benzaldehyde (15%), and aniline (17%). [The identity of the photo-

$$\underset{\mathbf{1}}{C_6H_5CH{=}NNHC_6H_5} \xrightarrow[CH_3OH]{h\nu} (C_6H_5)_2CH_2 + C_6H_5C{\equiv}N + C_6H_5NH_2 + C_6H_5CHO$$

products in this and subsequent reactions was established in each case by comparison of the spectral properties (ir, nmr, uv) of the photoproducts with those of independently obtained samples; where possible, mixture melting point comparisons were also made.] The remainder of the reaction mixture stayed as a dark brown band at the top of the chromatography column. Elution with several different solvents failed to move

(1) For paper VI, see J. I. Sarkisian and R. W. Binkley, *J. Org. Chem.*, **35**, 1228 (1970).

(2) Part of this work has been reported in a preliminary form; see R. W. Binkley, *Tetrahedron Lett.*, 1893 (1969).

(3) R. K. Brinton, *J. Amer. Chem. Soc.*, **77**, 842 (1955).

(4) J. F. Ogilvie, *Chem. Commun.*, 359 (1965).

(5) R. W. Binkley, *J. Org. Chem.*, **33**, 2311 (1968).

(6) G. Wettermark and A. King, *Photochem. Photobiol.*, **4**, 417 (1965).

(7) M. Padoa and T. Minganti, *Atti. Accad. Naz. Lincei., Mem., Cl. Sci. Fis. Mat. Natur. Sez. 2a*, **22**, 500 (1914).

(8) G. Condorelli and L. L. Costanzo, *Boll. Sedute Accad. Gioenia Sci. Natur. Catania*, **8** [4], 753 (1969).

this material. The course of reaction was not markedly altered by conducting the photolyses in the nonhydroxylic solvent benzene. Unfiltered irradiation of benzaldehyde phenylhydrazone (1) in methanol produced a reaction whose product yields were similar to, although generally lower than, those from the Vycor-filtered irradiation. Photolysis of a methanol solution of 1 through a Pyrex filter resulted in a gradual disappearance of starting material with benzaldehyde and aniline being the only products isolated. Benzaldehyde phenylhydrazone (1), as well as the other hydrazones studied, were subjected to the reaction conditions in the absence of light and found to be stable.

The photolysis of benzophenone hydrazone (2) in methanol under nitrogen through a Vycor filter produced, in addition to unreacted starting material, three products: benzophenone (34%), benzophenone imine (21%), and diphenylmethane (16%). The total yield of benzophenone and benzophenone imine was constant; however, the relative amounts of these two products fluctuated considerably. The yields men-

$$\underset{2}{(C_6H_5)_2C{=}NNH_2} \xrightarrow[CH_3OH]{h\nu} (C_6H_5)_2C{=}O + (C_6H_5)_2C{=}NH + (C_6H_5)_2CH_2$$

tioned for this reaction represent the highest percentage of benzophenone imine obtained. If the reaction mixture was allowed to stand overnight before work-up, no benzophenone imine was isolated. An independently synthesized sample of benzophenone imine[9] reverted upon standing overnight to benzophenone.[10] As with the irradiation of benzaldehyde phenylhydrazone (1), unfiltered photolysis of benzophenone hydrazone (2) yielded essentially the same result as the Vycor-filtered irradiation, although the yield of diphenylmethane decreased slightly. Photolysis of a mixture of hydrazine and benzophenone did not produce any of the reactions found from irradiation of benzophenone hydrazone (2). The only process observed in this mixed photolysis was a photoreduction reaction leading to benzpinacol.

Two different sets of reaction conditions had detectable effect upon the yield of diphenylmethane from irradiation of benzophenone hydrazone (2). The first of these consisted of conducting the photolyses of 2 in benzene where the yield of diphenylmethane increased to 39%. Unfortunately, the diphenylmethane formed during irradiation in benzene was difficult to separate from other hydrocarbon material which resulted from photochemical reactions of benzene itself. The second set of conditions which altered the yield of diphenylmethane from photolysis of 2 resulted when sodium hydroxide was added to the usual Vycor-filtered reaction in methanol. This modification increased the diphenylmethane yield to 31%.

Vycor-filtered irradiation of benzaldehyde diphenylhydrazone (3), the third in this series of hydrazones studied, resulted in formation of benzonitrile (30%) and carbazole (56%). No di- or triphenylmethane or di-

$$\underset{3}{C_6H_5CH{=}NN(C_6H_5)_2} \xrightarrow[CH_3OH]{h\nu} C_6H_5C{\equiv}N + \text{carbazole}$$

phenylamine[11] was detected in the reaction mixture. Similar Vycor-filtered irradiation of benzophenone phenylhydrazone (4) in methanol resulted in the isolation of benzophenone (19%) and aniline (17%) while benzophenone diphenylhydrazone (5) led to benzophenone (43%) and carbazole (76%).

$$\underset{4}{(C_6H_5)_2C{=}NNHC_6H_5} \xrightarrow[CH_3OH]{h\nu} (C_6H_5)_2C{=}O + C_6H_5NH_2$$

$$\underset{5}{(C_6H_5)_2C{=}NN(C_6H_5)_2} \xrightarrow[CH_3OH]{h\nu} (C_6H_5)_2C{=}O + \text{carbazole}$$

Discussion

Since one of the goals of the present study is a comparison between azine and hydrazone photochemistry, a logical place to begin discussion of the experimental findings from this work is with the similarities which exist between the photochemical reactions of these two systems. The major reaction pathway recorded for the various aldazines which already have been investigated begins with nitrogen–nitrogen bond cleavage in the azine system and ends with the formation of a nitrile and an imine[3-5] (Scheme I). The imine, in at least one case, hydrolyzes readily to the corresponding aldehyde.

Each of the five hydrazones investigated undergoes a photochemical reaction which is similar to the azine decomposition pictured in Scheme I. A ketone and an amine result from ketone hydrazone photolyses while an aldehyde, an amine, and a nitrile form when aldehyde hydrazones are irradiated. The carbonyl compounds isolated from these reactions appear to result from hydrolysis during isolation of imines formed during photochemical reaction. This proposed C=N to C=O conversion is supported by the fact that benzophenone imine can be isolated from the irradiation of benzophenone hydrazone (2) when the reaction is quickly analyzed; however, the imine thus isolated is converted to benzophenone simply upon standing in the air. A less rapid work-up of the benzophenone hydrazone (2) reaction mixture results only in isolation of benzophenone with no imine being detected. Benzaldimine, the imine anticipated from photolyses of hydrazones 1 and 3, has previously been shown to hydrolyze to benzaldehyde under the chromatographic conditions.[5] The similarity in product identity from azine and hydrazone photolyses suggests a similarity in reaction course.

Shown in Scheme II is a mechanistic proposal for the formation of aniline, benzaldehyde, and benzonitrile from the photolysis of benzaldehyde phenylhydrazone (1). A similar process is assumed to be operative in the formation of the corresponding products from photolyses of the other four hydrazones (2–5). To the extent that these two mechanisms (Schemes I and II) are correct, the most important photochemical reaction in both hydrazone and azine photochemistry is a nitrogen–nitrogen bond cleavage. The fact that this type of reaction is observed in the photochemistry of both hydrazones and azines suggests that in other types of compounds which contain a nitrogen–nitrogen single

(9) F. L. Pickard and T. L. Tolbert, *J. Org. Chem.*, **26**, 4886 (1961).
(10) A. Lachman, *Org. Syn.*, **10**, 28 (1930).
(11) Diphenylamine is converted photochemically to carbazole: see K. Grellmann, G. M. Sherman, and H. Linschitz, *J. Amer. Chem. Soc.*, **85**, 1882 (1963).

Scheme I
Formation of Nitriles and Imines from Aldazine Photolyses

$$RCH{=}NN{=}CHR \xrightarrow{h\nu} [RCH{=}N\cdot \quad \cdot N{=}CHR] \xrightarrow[\text{transfer}]{\text{hydrogen}} RC{\equiv}N + RCH{=}NH$$

hydrogen abstraction from solvent or other donor present

R = H, CH_3, C_6H_5

Scheme II
Formation of Aniline, Benzaldehyde, and Benzonitrile from Benzaldehyde Phenylhydrazone Photolysis

$$C_6H_5CH{=}NNC_6H_5 \xrightarrow{h\nu} [C_6H_5CH{=}N\cdot \quad \cdot NHC_6H_5] \xrightarrow[\text{transfer}]{\text{hydrogen}} C_6H_5C{\equiv}N + C_6H_5NH_2$$

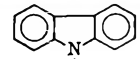
hydrogen solvent or ↓ abstraction from other donor present

$$C_6H_5NH_2 + C_6H_5CH{=}NH \xrightarrow{H_2O} C_6H_5CHO$$

Scheme III
Proposed Mechanism for Photochemical Wolff–Kishner Reduction

$$(C_6H_5)_2C{=}NNH_2 \xrightarrow{h\nu} \underset{2}{} [(C_6H_5)_2CHN{=}NH] \longrightarrow \underset{8}{} (C_6H_5)_2CH_2 + N_2$$

Table I
Photochemical Reactions of Hydrazones

Run	Hydrazone	Irradiation time, hr	Filter	% completion	Solvent	% yield of products[a]					
						$(C_6H_5)_2CH_2$	$C_6H_5C{\equiv}N$	C_6H_5CHO	$C_6H_5NH_2$		$(C_6H_5)_2CO$
1	Benzaldehyde (1) phenylhydrazone	2.0	Vycor[b]	68	Methanol	14	8	15	17		
2	Benzaldehyde (1) phenylhydrazone	2.0	Vycor	64	Benzene	14		12	7		
3	Benzaldehyde phenylhydrazone	1.0	None	52	Methanol	11	7	7	7		
4	Benzaldehyde (1) phenylhydrazone	22.0	Pyrex[c]	29	Methanol	None	None	19	Trace		
5	Benzophenone (2) hydrazone	4.0	Vycor	41	Methanol	26					34[d]
6	Benzophenone (2) hydrazone	4.0	Vycor	51	Methanol, NaOH	31					5[e]
7	Benzophenone (2) hydrazone	4.0	None	43	Methanol	16					17[f]
8	Benzophenone (2) hydrazone	4.0	Vycor	40	Benzene	39					45
9	Benzaldehyde (3) diphenylhydrazone	2.0	Vycor	100	Methanol		30			56	
10	Benzophenone (4) phenylhydrazone	4.0	Vycor	62	Methanol				17		19
11	Benzophenone (5) diphenylhydrazone	2.0	Vycor	100	Methanol					69	39

[a] Product yields based on reacted starting material. [b] Transmits above 205 nm. [c] Transmits above 280 nm. [d] 21% benzophenone imine isolated. [e] 48% benzophenone imine isolated. [f] 44% benzophenone imine isolated.

bond, photochemical cleavage of such a bond should be an expected process.[12]

It is worthwhile to compare the photochemical reactions of azines and hydrazones with their corresponding thermal reactions since the nitrogen–nitrogen bond scission process observed photochemically also appears to be important in thermal decompositions. From pyrolysis of aldazines, nitriles are formed[13] while similar

$$C_6H_5CH{=}NN{=}CHC_6H_5 \xrightarrow{300^\circ} C_6H_5C{\equiv}N + \text{other products}$$

$$\underset{\mathbf{1}}{C_6H_5CH{=}NNHC_6H_5} \xrightarrow{400^\circ} C_6H_5C{\equiv}N + C_6H_5NH_2 + \text{other products}$$

reaction of aldehyde phenylhydrazones results in both nitrile and amine formation;[14] thus, from the point of view of product identity, a clear similarity exists between the thermal and photochemical reactions of these systems. This similarity suggests that, in the case of azines and hydrazones, formation of an electronically excited state may lead, in part, to the same reaction pathway arrived at during thermal reaction.[15]

The second type of reaction encountered in the photolysis of hydrazones is one which has no analogy either in azine photochemistry or in the simple thermal reaction of hydrazones; however, there is analogy to this process in base-catalyzed hydrazone decomposition. This second reaction type is one which converts benzaldehyde phenylhydrazone (**1**) and benzophenone hydrazone (**2**) into diphenylmethane. Formation of diphenylmethane represents a reaction similar to the well-known Wolff–Kishner reduction of hydrazones to hydrocarbons in the presence of strong base. This photochemical Wolff–Kishner reduction potentially has a distinct advantage over its nonphotochemical counterpart in that the photochemical reaction is run under quite mild conditions (room temperature in neutral solution); hence, for compounds which are sensitive to the conditions of the normal Wolff–Kishner reduction, the photochemical reaction offers an attractive possible alternative.

A possible mechanism for the photochemical Wolff–Kishner reduction is given in Scheme III. The first step in this reaction sequence is a light-induced transfer of a hydrogen atom from the terminal nitrogen of the hydrazone system to the hydrazone carbon. Similar photochemical 1–3 hydrogen migrations are known to occur in related systems.[16] The second step in the proposed mechanism is the decomposition of the azo compound (**8**), producing diphenylmethane and nitrogen. This latter step is a characteristic reaction for azo systems of this type.[17]

Since only two of the five hydrazones studied experienced the photochemical Wolff–Kishner reduction, it is clear that definite requirements must be met by a hydrazone system in order for this reaction to take place. It is less certain, however, exactly what these requirements are; in fact, one area of continuing investigation of hydrazone photochemistry is concerned with determining, in general, which type of hydrazone will undergo this photochemical reduction.[18] From the five systems studied it appears that one feature which is necessary for this reaction to occur is the presence of at least one hydrogen atom on the terminal nitrogen of the hydrazone system; however, this clearly is not the only requirement since benzophenone phenylhydrazone (**4**) contains such a hydrogen but does not undergo the light-induced reaction.

Although mention has been made of the advantage of the photochemical Wolff–Kishner reaction over its nonphotochemical counterpart, two possible disadvantages also should be noted. The first of these is that the photochemical hydrazone to hydrocarbon conversion occurs in fairly low yield; in fact, the best yield for this reaction, obtained for the photochemical conversion of benzophenone hydrazone (**2**) to diphenylmethane in benzene, was slightly less than 40%. The second uncertainty concerning the photochemical Wolff–Kishner reduction relates to the generality of this process, since as was mentioned in the preceding paragraph, this reaction has been observed for only two hydrazones at present.

In conclusion, then, it appears that the formation of several different types of products from the photolysis of hydrazones is understandable in terms of two basic reaction pathways. The first of these is a fragmentation of the hydrazone system into an imine, an amine, and a nitrile while the second reaction type brings about a hydrazone to hydrocarbon conversion. The latter of these two reactions, a photochemical Wolff–Kishner reduction, is a potentially useful synthetic process.

Experimental Section

Vycor-Filtered Irradiation of Benzaldehyde Phenylhydrazone (1) in Methanol.—Benzaldehyde Phenylhydrazone[19] (425.0 mg, 2.168 mmol) in 390 ml of methanol was irradiated for 2.0 hr with a 450-W Hanovia high-pressure quartz mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. Prepurified nitrogen was passed through the solution for 1.0 hr prior to irradiation and a slow stream of nitrogen was continued during photolysis. A Vycor filter was placed between the reaction mixture and the light source.

After 2.0 hr, the solvent was removed by distillation *in vacuo* below 35°, leaving a red-brown solid and producing a distillate which was transparent in the uv region. The residual solid was chromatographed on an 80 × 2.5 cm Florisil column slurry packed in 1:9 ether–hexane; 60-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane, 0.5 l. of 1:49 ether–hexane, 0.5 l. of 1:24 ether–hexane, 0.5 l. of 1:12 ether–hexane, 0.5 l. of 1:6 ether–hexane, 0.5 l. of 1:3 ether–hexane, 0.5 l. of 1:1 ether–hexane, and 0.5 l. of ether.

(12) Several reactions, involving other types of systems, in which photochemical nitrogen–nitrogen bond cleavage reaction has occurred have been reported: for example, K. Akiba, I. Fukawa, K. Mashita, and N. Inanoto, *Tetrahedron Lett.*, 2859 (1968); V. Snieckus, *Chem. Commun.*, 831 (1969); P. Flowerday and M. J. Perkins, *J. Amer. Chem. Soc.*, **91**, 1036 (1969). It is important to note that while photochemical cleavage of a nitrogen–nitrogen single bond promises to be a frequently occurring process, some systems which are capable of such behavior exist but do not react in this way. E. J. Volker and J. A. Moore, *J. Org. Chem.*, **34**, 3639 (1969); B. Singh, *J. Amer. Chem. Soc.*, **91**, 3671 (1969); S. N. Ege, *Chem. Commun.*, 759 (1968).

(13) H. E. Zimmerman and S. Somasekhara, *J. Amer. Chem. Soc.*, **87**, 5865 (1960).

(14) W. D. Crow and R. K. Solly, *Aust. J. Chem.*, **19**, 2119 (1966).

(15) While a similarity in reaction products may suggest a similarity in mechanism between photochemical and thermal reaction, much more evidence is necessary to establish such a proposal. In fact, the work of Crow and Solly (ref 14) has led them to postulate a quite different mechanism for the thermal decomposition of hydrazones than that proposed here for their photochemical reaction.

(16) (a) M. J. Jorgenson, *J. Amer. Chem. Soc.*, **91**, 6432 (1969); (b) M. J. Jorgenson, *Chem. Commun.*, 137 (1965); (c) M. J. Jorgenson and L. Grundel, *Tetrahedron Lett.*, 4991 (1968).

(17) E. M. Kosower, P. C. Huang, and T. Tsuji, *J. Amer. Chem. Soc.*, **91**, 2325 (1969).

(18) R. W. Binkley and A. S. Kushner, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, ORGN 15.

(19) E. Fischer, *Ber.*, **9**, 887 (1876).

Fractions 8–11 yielded 35 mg (0.21 mmol, 14%) of diphenylmethane, identical in ir and nmr spectra with an authentic sample[20] of diphenylmethane. Fractions 20–24 gave 5 mg of a deep red solid which was not further characterized. Fractions 33–36 afforded 23 mg (0.22 mmol, 15%) of benzaldehyde, identical in ir and uv spectra with an authentic sample[20] and forming, according to the method of Shriner, Fuson, and Curtin,[21] benzaldehyde semicarbazone, mp 219–222° (lit.[22] mp 222°). Fractions 37 and 38 produced 12 mg (0.12 mmol, 8%) of benzonitrile, identical in ir and uv spectra with a known sample of benzonitrile.[20] Fractions 42–50 gave 147 mg of yellow solid, mp 140–149°, recrystallized from ethanol–water to give 137 mg (0.698 mmol) of yellow crystalline benzaldehyde phenylhydrazone (1), mp 154–155° (lit.[19] mp 153°). Fractions 52–56 afforded 23 mg (0.25 mm) of yellow oil identical in ir spectrum with a known sample of aniline[20] and forming, upon reaction with benzoyl chloride, benzanilide, mp 160° (lit.[23] mp 163°).

Pyrex-Filtered Irradiation of Benzaldehyde Phenylhydrazone (1) in Methanol.—Benzaldehyde Phenylhydrazone (221 mg, 1.12 mmol) was irradiated under exactly the same conditions as described for the Vycor-filtered irradiation in methanol except that a Pyrex filter was placed between the lamp and the reaction mixture and the irradiation time was increased to 22.0 hr. The chromatographic procedure was also the same as that described above.

The first 20 fractions contained no material. Fractions 21–24 gave 7 mg of a deep red solid, which was shown by tlc analysis to contain at least two compounds. This red material was not further characterized. Fractions 37–38 afforded 7 mg (0.07 mmol, 19%) of benzaldehyde, identified by ir spectroscopy. Fractions 39–47 yielded 156 mg (0.79 mmol) of benzaldehyde, phenylhydrazone (1), mp 150–154°. Fractions 50–55 gave a trace (less than 2 mg) of material which had the same uv spectrum as aniline.

Direct Irradiation of Benzaldehyde Phenylhydrazone (1) in Methanol.—Benzaldehyde phenylhydrazone (483.4 mg, 2.46 mmol) was irradiated under the same conditions as the Vycor-filtered irradiation of 1 except that no filter was used and the irradiation time was reduced to 1.0 hr. The chromatographic procedure was the same as that described above.

Fractions 6–10 gave 25 mg (0.15 mmol, 11%) of diphenylmethane, identified by ir spectroscopy. Fractions 17–21 gave 3 mg of red solid which was not identified. Fractions 30–32 produced 10 mg (0.09 mmol, 7%) of benzaldehyde, identified by ir and uv spectroscopy. Fractions 33 and 34 afforded 10 mg (0.09 mmol, 7%) of benzonitrile, identified by ir and uv spectroscopy. Fractions 38–48 gave 280 mg of yellow-brown solid, mp 131–139°, recrystallized from ethanol–water to give 264 mg (1.34 mmol) of benzaldehyde phenylhydrazone, mp 154°. Fractions 50–52 yielded 9 mg (0.09 mmol, 7%) of aniline, identified by ir spectroscopy.

Vycor-Filtered Irradiation of Benzaldehyde Phenylhydrazone (1) in Benzene.—Benzaldehyde phenylhydrazone (3.964 mg, 2.02 mmol) was irradiated under the same conditions as in the Vycor-filtered irradiation in methanol except that benzene was used as the reaction solvent. The chromatographic procedure was also the same.

Fractions 7–14 afforded 93.2 mg of colorless oil which appeared by ir spectroscopy to be impure diphenylmethane. These fractions were rechromatographed (see below). Fractions 22–25 gave 5 mg of a deep red solid which was not examined further. Fractions 35–40 yielded 16 mg (0.16 mmol, 12%) of benzaldehyde, identified by ir spectroscopy. Fractions 42–49 gave 254 mg (1.29 mmol) of benzaldehyde phenylhydrazone, mp 150–155°. Fractions 55–60 produced 9 mg (0.09 mmol, 7%) of aniline, identified by ir spectroscopy.

Rechromatography of fractions 7–14 from the above chromatography column in the same manner on silicic acid gave 17 mg (0.10 mmol, 14%) of diphenylmethane, identified by ir spectroscopy, in fractions 8–10.

Stability Test of Benzaldehyde Phenylhydrazone (1) under Reaction and Isolation Conditions.—Benzaldehyde phenylhydrazone (216.2 mg, 1.10 mmol) was subjected to the same reaction and isolation conditions as described in the Vycor-filtered irradiation in methanol except that the lamp was not turned on. Unreacted starting material was recovered quantitatively.

Vycor-Filtered Irradiation of Benzaldehyde Diphenylhydrazone (3) in Methanol.—Benzaldehyde diphenylhydrazone[24] (271.1 mg, 0.995 mmol) was irradiated in the same way as described for the Vycor-filtered irradiation of benzaldehyde phenylhydrazone in methanol. The chromatography procedure was also the same.

The first 27 fractions contained no material. Fractions 28–36 yielded 92 mg (0.56 mmol, 56%) of carbazole, mp 244° (lit.[25] mp 238°). The photochemically produced carbazole was identical in ir spectrum and showed no mixture melting point depression with an authentic sample.[20] Fractions 38–41 afforded 31 mg (0.30 mmol, 30%) of benzonitrile, identified by ir spectroscopy.

Stability Test of Benzaldehyde Diphenylhydrazone (3) under Reaction and Isolation Conditions.—Benzaldehyde diphenylhydrazone (3) was subjected to the same reaction and isolation conditions as described in the Vycor-filtered irradiation in methanol except that the lamp was not turned on. Unreacted starting material was recovered quantitatively.

Vycor-Filtered Irradiation of Benzophenone Phenylhydrazone (4) in Methanol.—Benzophenone phenylhydrazone[26] (504.4 mg, 1.85 mmol) was irradiated in the same manner as that described for the Vycor-filtered irradiation of benzalaldehyde phenylhydrazone (1) in methanol except that the irradiation time was 4.0 hr. The chromatographic procedure was the same as in the previous experiments.

Fractions 1–15 contained no material. Fractions 16–23 yielded 194 mg of unreacted benzophenone phenylhydrazone (4), mp 132–135° (lit.[26] mp 137°). Fractions 30–35 afforded 23 mg (0.27 mmol, 19%) of benzophenone, identified by ir spectroscopy. Fractions 50–55 afforded 23 mg (0.24 mmol, 17%) of aniline, identified by ir spectroscopy.

Stability Test of Benzophenone Phenylhydrazone (4) under Reaction and Isolation Conditions.—Benzophenone phenylhydrazone was subjected to the same reaction and isolation conditions as described in the Vycor-filtered irradiation of benzaldehyde phenylhydrazone (1) in methanol except that the lamp was not turned on. Unreacted starting material was recovered quantitatively.

Vycor-Filtered Irradiation of Benzophenone Diphenylhydrazone (5) in Methanol.—Benzophenone diphenylhydrazone[27] (359.6 mg, 1.03 mmol) was irradiated in the same manner as described for the Vycor-filtered irradiation of benzaldehyde phenylhydrazone (1) in methanol. The chromatographic procedure was also the same.

The first 18 fractions contained no material. Fractions 19–21 gave 7 mg of unreacted benzophenone diphenylhydrazone, mp 139–145° (lit.[27] mp 145°). Fractions 30–35 yielded 130 mg (0.78 mmol, 76%) of carbazole, mp 240–244°, identical in ir spectrum with an independent sample. Fractions 36–42 afforded 80 mg (0.44 mmol, 43%) of benzophenone, identified by ir spectroscopy.

Stability Test of Benzophenone Diphenylhydrazone (5) under Reaction and Isolation Conditions.—Benzophenone diphenylhydrazone was subjected to the same reaction and isolation conditions as described in the Vycor-filtered irradiation of benzaldehyde phenylhydrazone (1) in methanol except that the lamp was not turned on. Unreacted starting material was recovered quantitatively.

Vycor-Filtered Irradiation of Benzophenone Hydrazone (2) in Methanol.—Benzophenone hydrazone[20] (385.2 mg, 1.97 mmol) was irradiated in the same manner as described for the Vycor-filtered irradiation of benzaldehyde phenylhydrazone (1) in methanol except that the irradiation time was 4.0 hr. The chromatographic procedure was the same as in the previous experiments.

Fractions 8–11 yielded 28 mg (0.17 mmol, 26%) of diphenylmethane, identified by ir and nmr spectra. Fractions 34–38 gave 39 mg (0.22 mmol, 34%) of benzophenone, identified by comparison of the ir and uv spectra. Fractions 43–48 gave 24 mg (0.13 mmol, 21%) of benzophenone imine, identical in ir spectrum with that of an independently prepared sample[9] and decomposing to benzophenone upon standing in the air. Frac-

(20) Aldrich Chemical Co., Inc., Milwaukee, Wis. 53210.

(21) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1956, pp 218, 283.

(22) J. Thiele, *Justus Liebigs Ann. Chem.*, **270**, 34 (1892).

(23) H. Hubner, *ibid.*, **208**, 291 (1881).

(24) E. Fischer, *ibid.*, **190**, 179 (1878).

(25) C. Graebe and C. Glaser, *Ber.*, **5**, 12 (1872).

(26) M. Pickel, *Justus Liebigs Ann. Chem.*, **232**, 228 (1886).

(27) W. Schlenk and E. Bergmann, *ibid.*, **463**, 311 (1928).

tions 50–59 gave 260 mg (1.17 mmol) of unreacted benzophenone hydrazone, mp 95–96° (lit.[28] mp 98°).

Direct Irradiation of Benzophenone Hydrazone (2) in Methanol.—Benzophenone hydrazone (476 mg, 2.46 mmol) was irradiated in the same manner as described for the Vycor-filtered irradiation of benzaldehyde phenylhydrazone (1) in methanol except that no filter was used and the irradiation time was extended to 4.0 hr. The chromatographic procedure was the same as in the previous experiments.

Fractions 7–10 yielded 28 mg (0.17 mmol, 16%) of diphenylmethane, identified by ir and nmr spectroscopy. Fractions 35–39 gave 33 mg (0.18 mmol, 17%) of benzophenone, identified by ir spectroscopy. Fractions 45–51 gave 83 mg (0.46 mmol, 44%) of benzophenone imine, identified by ir spectroscopy and by spontaneous conversion to benzophenone upon standing. Fractions 52–59 produced 273 mg (1.39 mmol) of unreacted benzophenone hydrazone, mp 94–97°.

Vycor-Filtered Irradiation of Benzophenone Hydrazone (2) in Benzene.—Benzophenone hydrazone (339.1 mg, 1.73 mmol) was irradiated in the same manner as described for the Vycor-filtered irradiation of benzaldehyde phenylhydrazone (1) in methanol except that benzene was the reaction solvent and the irradiation time was extended to 4.0 hr. The chromatographic procedure was the same as in the previous experiments.

Fractions 5–10 gave 69 mg of material whose ir spectrum indicated it to be impure diphenylmethane. These fractions were rechromatographed (see following paragraph). Fractions 29–34 afforded 56 mg (0.31 mmol, 45%) of benzophenone, identified by ir spectroscopy. Fractions 43–50 produced 204 mg (1.04 mmol) of unreacted benzophenone hydrazone, mp 92–94°.

Rechromatography of fractions 5–10 under the same conditions gave 39 mg (0.23 mmol, 39%) of diphenylmethane, identified by ir spectroscopy, in fractions 5–8.

Vycor-Filtered Irradiation of Benzophenone Hydrazone (2) in Methanol Containing Sodium Hydroxide.—Benzophenone hydrazone (398 mg, 2.03 mmol) and sodium hydroxide (20 mg, 0.50 mmol) were irradiated in the same manner as described for the Vycor-filtered irradiation of 1 in methanol. The chromatographic analysis of the reaction mixture was also conducted in the same manner.

Fractions 6–8 afforded 53 mg (0.32 mmol, 31%) of diphenylmethane, identified by ir spectroscopy. Fractions 29–31 gave 9 mg (0.05 mmol, 5%) of benzophenone, identified by ir spectroscopy. Fractions 33–39 produced 89 mg (0.49 mmol, 48%) of benzophenone imine, identified by ir spectroscopy and by conversion to benzophenone upon standing. Fractions 42–52 gave 197 mg of unreacted benzophenone hydrazone (2), mp 90–94°.

Pyrex-Filtered Irradiation of Benzophenone and Hydrazine in Benzene.—Benzophenone (180 mg, 1.00 mmol) and hydrazine (128 mg, 4.00 mmol) were irradiated in the same manner as described for the Pyrex-filtered irradiation of 1 except that benzene was the solvent. The ir spectrum of the crude reaction mixture was the same as that of benzopinacol.

Registry No.—1, 588-64-7; 2, 5350-57-2; 3, 966-88-1; 4, 574-61-8; 5, 3746-21-2.

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(28) T. Curtius and E. Rauterberg, *J. Prakt. Chem.*, **44** [2], 194 (1891).

Reactions of Ketones and Related Compounds with Solid Supported Phosphoric Acid Catalyst. IV. Rearrangement Studies of Trimethylacetaldehyde-1-^{14}C and 3-Methyl-2-butanone-2-^{14}C[1]

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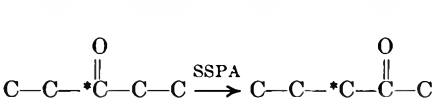
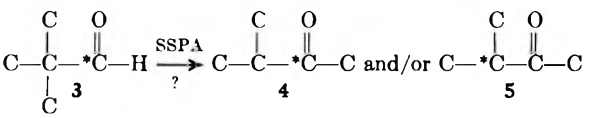
Solid supported phosphoric acid (SSPA) treatment of trimethylacetaldehyde-1-^{14}C at 230° gives 3-methyl-2-butanone-2-^{14}C (4) and no 3-methyl-2-butanone-3-^{14}C (5); no oxygen-function rearrangement takes place. Further SSPA treatment of 4 did not result in rearrangement to 5. These and related experiments where oxygen-function rearrangement does take place are rationalized in terms of relative stabilities of proposed carbonium ion intermediates.

Solid supported phosphoric acid (SSPA) is an effective catalyst for the rearrangement of aldehydes and ketones to isomeric ketones.[2] In agreement with previous work,[3] trimethylacetaldehyde was found[2] to rearrange quantitatively to 3-methyl-2-butanone.

Since the 2-pentanone formed from 3-pentanone-3-^{14}C (1) by SSPA treatment had all of the carbon-14



label in the 3 position,[4] it was of interest to see if a similar oxygen-function rearrangement would take place in the SSPA-catalyzed rearrangement of trimethylacetaldehyde to 3-methyl-2-butanone.



Trimethylacetaldehyde-1-^{14}C (3), synthesized by the method of Brown and Tsukamoto,[5] was passed once through a SSPA column[2] at 230°, and the resulting 3-methyl-2-butanone-X-^{14}C was degraded to isopropyl acetate by *m*-chloroperbenzoic acid oxidation. Derivatives of the acid and alcohol parts of the ester were prepared and assayed for radio activity. The results of these experiments are shown in Table I.

Since all of the radioactivity was found in the acetanilide and none in the isopropyl derivative, it is clear that oxygen-function rearrangement does not take place during the conversion of trimethylacetaldehyde to 3-methyl-2-butanone, *i.e.*, **3** → **4** and not **5**.

(1) Supported by U. S. Atomic Energy Commission Contract AT-(40-1)-3234. Paper III in this series: F. Juge and A. Fry, *J. Org. Chem.*, **35**, 1876 (1970).

(2) W. H. Corkern and A. Fry, *J. Amer. Chem. Soc.*, **89**, 5888 (1967).

(3) S. N. Danilov and E. D. Venus-Danilova, *Ber.*, **59B**, 377 (1926); H. Hopff C. D. Nenitzescu, D. A. Isacescu, and I. P. Cantuniari, *ibid.*, **69B**, 2244 (1936).

(4) A. Fry and W. H. Corkern, *J. Amer. Chem. Soc.*, **89**, 5894 (1967).

(5) H. C. Brown and A. Tsukamoto, *ibid.*, **83**, 4549 (1961).

TABLE I

ACTIVITY RESULTS (MILLICURIE/MOLE) FOR THE SSPA REARRANGEMENT OF TRIMETHYLACETALDEHYDE-1-^{14}C TO 3-METHYL-2-BUTANONE-X-^{14}C

Expt	Trimethylacetaldehyde-1-^{14}C[a]	3-Methyl-2-butanone-X-^{14}C[a]	Acetanilide	Isopropyl 3,5-dinitrobenzoate
1	0.0087 ± 0.00005	Not determined	0.0086 ± 0.00003	0.0001[b]
2	0.364 ± 0.001	0.365 ± 0.005	0.365 ± 0.001	0.0008 ± 0.00007

[a] The activities of the aldehyde and ketone were determined on the semicarbazone derivatives. [b] Indistinguishable from the counting rate for blank samples.

TABLE II

ACTIVITY RESULTS (MILLICURIE/MOLE) OBTAINED BY REPEATED PASSAGE OVER SSPA CATALYST AT 230° OF THE 3-METHYL-2-BUTANONE FORMED FROM TRIMETHYLACETALDEHYDE-1-^{14}C

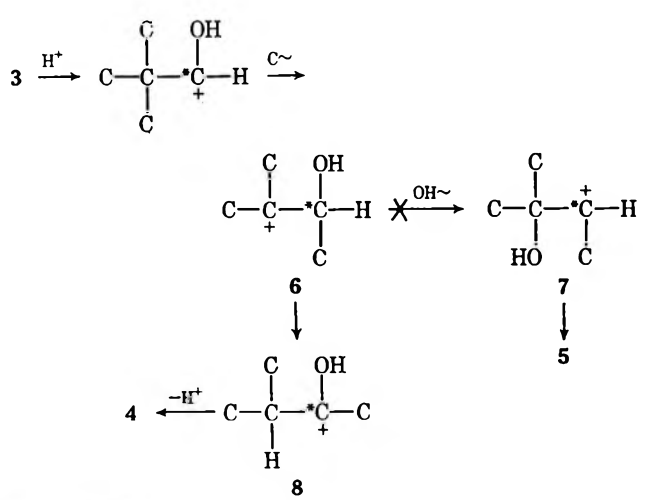
No. of passes over SSPA	Recovered material, ml	Removed for degradation, ml	Acetanilide	Isopropyl 3,5-dinitrobenzoate
0[a]	32			
1	28	6	0.206 ± 0.001	0.0004 ± 0.0001
2	20			
3	20	5	0.205 ± 0.001	0.0005 ± 0.0001
4	13			
5	13			
6	13	5	0.206 ± 0.001	0.001 ± 0.0001
7	7			
8	7			
9	5	5	0.206 ± 0.001	0.001 ± 0.0001

[a] The radioactivity of trimethylacetaldehyde-1-^{14}C used was 0.206 ±0.001 mCi/mol, and 3-methyl-2-butanone obtained after one pass was 0.206 ± 0.001 mCi/mol. The activities of the aldehyde and ketone were determined on the semicarbazone derivatives.

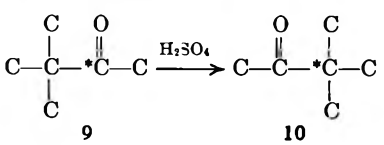
The possibility that the first formed 3-methyl-2-butanone-2-^{14}C (**4**) might undergo oxygen-function rearrangement (equilibration of **4** and **5**) upon longer exposure to the SSPA catalyst was then checked with the results shown in Table II.

Again, all of the radioactivity remains in the carbonyl group; **4** does not equilibrate with **5**; oxygen-function rearrangement is not observed, in sharp contrast to the formation of **2** from **1**. The possibility that **4** would form **5** at the higher temperature (340° compared with 230°) used[4] in the conversion of **1** to **2** could not be checked because such branched-chain compounds decompose readily at the higher temperature.[2]

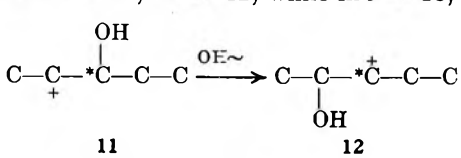
The most likely path for the rearrangement of **3** to **4** may be depicted as follows,[6] the critical question being the relative rate of hydrogen migration (**6** → **8**) *vs.* oxygen-function rearrangement (here depicted as OH migration for simplicity) (**6** → **7**). It may be noted that **6** → **7** involves the energetically unfavorable conversion of a tertiary carbonium ion (3° R^+) to a secondary carbonium ion (2° R^+) while **6** → **8** represents the energetically more favorable conversion of a 3°R^+ to a highly stabilized ketone conjugate acid.

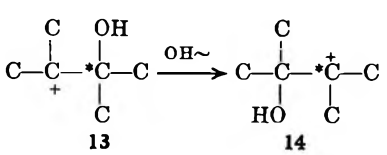


The lack of oxygen-function rearrangement in **4**, its presence[4] in **1** → **2**, and its presence[7] in the sulfuric acid catalyzed rearrangement of 3,3-dimethyl-2-butanone-2-^{14}C (**9**) to 3,3-dimethyl-2-butanone-3-^{14}C (**10**) may be



rationalized in a similar fashion. In **1** → **2**, the process corresponding to the energetically unfavorable 3° R^+ **6** → 2° R^+ **7** involves interconversion of two energetically similar 2° R^+, **11** → **12**, while in **9** → **10**, the corresponding step involves interconversion of two energetically identical 3° R^+, **13** → **14**.





Experimental Section

Trimethylacetaldehyde-1-^{14}C (3).—Trimethylacetic acid-1-^{14}C was prepared by carbonation of *t*-butylmagnesium chloride with carbon-14 dioxide by standard methods. The acid was converted to the acid chloride by exchange with benzoyl chloride,[8] and then to trimethylacetaldehyde-1-^{14}C, bp 72-74° (730 mm) [lit.[5] bp

(6) In this and the following formulations, the ions are shown as open carbonium ions without specific discussion at this time of the accompanying solvation, counterions, *etc.*

(7) K. Bhatia and A. Fry, *J. Org. Chem.*, **34**, 806 (1969).

(8) H. C. Brown, *J. Amer. Chem. Soc.*, **60**, 1325 (1938).

73–75° (740 mm)], semicarbazone mp 190° (lit.[9] mp 191°) by the method of Brown and Tsukamoto.[5] The radiochemical purity of **3** is adequately demonstrated by the agreement in the radioactivity values for **3** and **4** and by the excellent activity balances in the degradation products of **3** and **4** as shown in Tables I and II.

Rearrangement of Trimethylacetaldehyde-1-^{14}C and Treatment of 3-Methyl-2-butanone-2-^{14}C (4) with SSPA.—Preparation of the SSPA catalyst and the general experimental procedure have been described previously.[2] A column temperature of 230° was used, and, after one pass of 10 ml of **3** over the catalyst, the 8.7 ml of liquid recovered was shown by glpc and nmr analysis to be free of **3** and to consist entirely of 3-methyl-2-butanone, semicarbazone mp 113° (lit.[10] mp 114°). A 32-ml sample of **3** and the products from its rearrangement were passed repeatedly over the SSPA catalyst at 230°. Samples of the material recovered from passes one, three, six, and nine (Table II) were subjected to glpc and nmr analysis, and were degraded to check for oxygen-function rearrangement of the 3-methyl-2-butanone produced in the first pass. Small amounts of impurities were detected in the later fractions, but these were removed in the work-up and degradation procedures.

Degradation of 3-Methyl-2-butanone-2-^{14}C (4).—Oxidation of **4** to isopropyl acetate and derivative preparation from the ester were carried out as described previously[4,7] except that the more stable, commercially available *m*-chloroperbenzoic acid was used instead of perbenzoic acid. The isopropyl acetate was purified by distillation, bp 88° (740 mm) (lit.[11] bp 91°), and identified by glpc and nmr comparison with an authentic sample. A careful search (glpc analysis) was made for the isomeric ester, methyl isobutyrate, but none was found. Acetanilide, mp 113.5° (lit.[12] mp 114°), and isopropyl 3,5-dinitrobenzoate, mp 122°, (lit.[13] mp 122°), were obtained from the degradation.

Radioactivity Measurements.—The semicarbazones of **3** and **4** and the acetanilide and isopropyl 3,5-dinitrobenzoate derivatives of the degradation products of **4** were assayed for carbon-14 content using a Beckman LS100 liquid scintillation counter, and the external standard ratio method.[14] The results of the activity determinations are given in Tables I and II. The indicated errors are average deviations of three or more measurements of the same sample.

Registry No.—**3**, 24454-13-5; **4**, 24454-14-6.

(9) S. I. Heilbron, Ed., "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965, p 1214.

(10) Reference 9, p 2144.

(11) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 302.

(12) Reference 11, p 276.

(13) Reference 11, p 280.

(14) For full details of this procedure, see B. W. Palmer, Ph.D. Dissertation, University of Arkansas, Fayetteville, Ark., 1970.

Reaction of 2-(Δ³-Cyclopentenyl)ethyl Bromide with Tri-*n*-butyltin Hydride. Cyclization to Norbornane[1]

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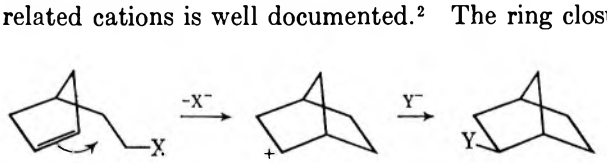
Received January 28, 1970

The reduction of 2-(Δ³-cyclopentenyl)ethyl bromide (**1**) with tri-*n*-butyltin hydride proceeds with some cyclization to norbornane (**3**). At 130° with dilute hydride the cyclization is appreciable. The cyclization process is discussed in terms of purportedly delocalized intermediates in the analogous cationic process. The conclusion is reached that successful cyclization of 2-(Δ³-cyclopentenyl)ethyl substrates does not necessarily indicate delocalized *intermediates*. Rather, a favorable geometry in the *transition state* for both cationic and radical (but not the anionic) processes rationalizes the data.

The so-called "π route" (1) to the 2-norbornyl and related cations is well documented.[2] The ring closure



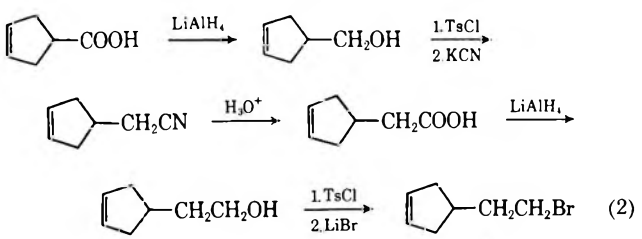
(1)

observed in spite of the considerable steric strain involved (estimated[3] at 9–19 kcal mol^{-1}) has been taken[2b] as evidence for the special stability associated with the 2-norbornyl cation, a stability commonly attributed to its supposed nonclassical nature.

Although ring closure of carbon radicals is likewise well documented,[4] we have found no such study extant comparable to eq 1. In line with our interest in possible nonclassical radicals,[5] we studied the 2-(Δ³-cyclopentenyl) ethyl radical (**1**·) to seek ring-closed products.

Results and Discussion

2-(Δ³-Cyclopentenyl)ethyl bromide (**1**) was prepared from the corresponding tosylate by treatment with lithium bromide in dry acetone (eq 2). The synthetic



(2)

1

sequence proceeded from 3-cyclopentene-1-carboxylic acid and utilized known procedures (see Experimental Section). Bromide **1** so prepared was characterized by

(1) Taken from the M.S. Thesis of S. N. M., Loyola University of Chicago, 1969.

(2) (a) R. G. Lawton, *J. Amer. Chem. Soc.*, **83**, 2399 (1961); (b) P. D. Bartlett and S. Bank, *ibid.*, **83**, 2591 (1961); (c) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *ibid.*, **87**, 1288 (1965); (d) H. L. Goering and W. D. Closson, *ibid.*, **83**, 3511 (1961); (e) S. Winstein and P. Carter, *ibid.*, **83**, 4485 (1961).

(3) Bartlett and Bank[2b] give the strain energy of the norbornyl ring as "about 19" kcal mol^{-1} and quote a privately communicated estimate from H. J. Dauben, Jr., as 9.49 kcal mol^{-1}. From heat of combustion data, 18.5 kcal mol^{-1} appears most reliable: A. F. Bedford, A. E. Beezer, C. T. Mortimer, and H. D. Springall, *J. Chem. Soc.*, 3823 (1963).

(4) For recent references, *cf.* (a) D. L. Struble, A. L. J. Beckwith, and G. E. Green, *Tetrahedron Lett.*, 3701 (1968); (b) M. Julia and M. Maumy, *Bull. Soc. Chim. Fr.*, **4**, 1603 (1968).

(5) J. W. Wilt and A. A. Levin, *J. Org. Chem.*, **27**, 2319 (1962); J. W. Wilt, G. Gutmar, W. J. Ranus, Jr., and A. R. Zigman, *ibid.*, **32**, 893 (1967).

TABLE I

REACTION OF 1 WITH TRI-*n*-BUTYLTIN HYDRIDE[a]

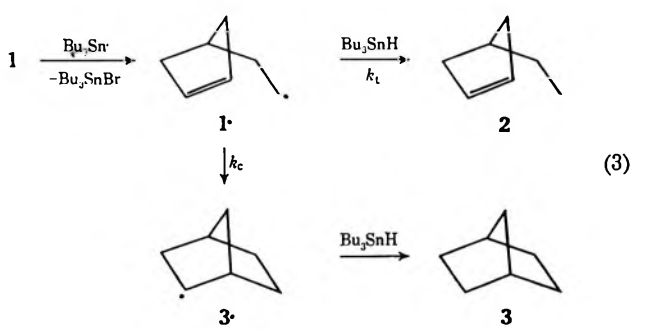
Bu_3SnH, M	Temp, °C	Product composition[b,c] 4-Ethylcyclopentene (2)	Norbornane (3)
0.100	93[d]	93	7
0.050	93	86	14
0.025	93	80	20
0.100	130[e]	82	18
0.050	130	75	25
0.025	130	59	41

[a] Bromide 1 was in threefold excess in all runs. [b] Only traces at most of norbornane were formed at 40° (AIBN initiated) at the three concentrations of Bu_3SnH used. [c] The conversions allowed were small (*ca.* 10–20%) so as to simplify the kinetics (see Text) and to prevent loss of 2 through addition of Bu_3SnH. Several runs were made at each temperature and the percentages are ± 1%. [d] AIBN initiated. [e] Di-*t*-butyl peroxide initiated.

combustion analysis and consonant spectra.[6] To produce 1·, we chose the excellent process developed by Kuivila, *viz.*, reduction with tri-*n*-butyltin hydride.[7]

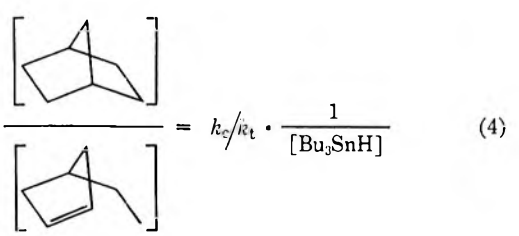
The reduction of 1 was patterned after the study by Walling, *et al.*,[8] of 6-bromo-1-hexene. The results are gathered in the Table I.

Clearly, the "π route" to ring closure occurs in the radical case also.[9] The most economical[10] pathway from 1 to products is given in eq 3. With the low



(3)

conversions allowed in this work, one may consider that $[Bu_3SnH] \cong$ constant. Following an approach used in similar situations,[11] one may then derive eq 4.

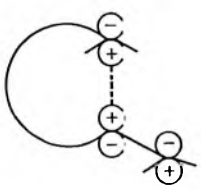


$$= k_c/k_t \cdot \frac{1}{[Bu_3SnH]} \qquad (4)$$

From the data in the Table, $k_c/k_t \cong 19 \times 10^{-3}$ at 130°, whereas at 93° this ratio is understandably smaller, 7.3×10^{-3}. An Arrhenius treatment of these ratios indicates that the cyclization of 1· to 3· has an energy barrier *ca.* 7.6 kcal mol^{-1} above that for the transfer process leading to 2. Carlsson and Ingold[12] have found rate constants of 10^5–10^6 M^{-1} sec^{-1} for chain transfer with organotin hydrides at 25° (a calculated energy barrier of 6.8–8.2 kcal mol^{-1}); so the barrier involved in the cyclization of 1· to 3· is *ca.* 14–16 kcal mol^{-1}. While we have no direct evidence on the overall enthalpy change associated with this ring closure, we judge it to be modestly exothermic. An approximate calculation[13] gave $\Delta H \cong -9$ kcal mol^{-1}.

Such a cyclization in spite of the strain involved might be viewed as evidence for unusual stability in 3·, as has been the claim for the analogous cationic process.[2b] No available evidence supports this view, however. Indeed, the consensus is that 3· is a classical radical devoid of extraordinary stabilization *via* 1, 6-σ or other electronic delocalization.[14] We therefore conclude that cyclization of 2-(Δ^3-cyclopentenyl)ethyl substrates to norbornyl products does not *per se* require nonclassicality in the cyclized intermediate.[15]

An explanation for the cyclization centers on the mechanism proposed by Struble, *et al.*,[4] namely, an interaction of the radical center with the π^* orbital of the double bond along a line vertical with one of the olefinic carbon atoms (5). Such a vertical bond-forming path



(5)

helps to explain the curious fact[4] that such cyclizations preferentially form five-membered rather than the thermodynamically preferred six-membered ring products even at the expense of a primary radical intermediate. In the case of 1· such a path (6) could involve a transition state (i or i′ equally) utilizing vertical bond formation *or* possibly the symmetric one (ii) also shown which does not. Interestingly, the analogous cyclization of the 2-(Δ^3-cyclopentenyl)ethyl anion does not occur.[6] Simple molecular orbital calculations[16] indicate that a tricentric transition state involving two or three electrons is favored when triangular (as would be ii). With

(6) E. A. Hill, R. J. Thiessen, A. Doughty, and R. Miller, *J. Org. Chem.*, **34**, 3681 (1969), reported this without analysis. Their sample was prepared from the corresponding alcohol and phosphorus tribromide in pyridine and contained some impurities, among them norbornyl bromide (~5%). Our material showed no contamination (glpc and spectra). Otherwise their reported properties and spectra for 1 agree with ours (see Experimental Section).

(7) H. G. Kuivila, L. W. Menapace, and C. R. Warner, *J. Amer. Chem. Soc.*, **84**, 3584 (1962); L. W. Menapace and H. G. Kuivila, *ibid.*, **86**, 3047 (1964); H. G. Kuivila, *Accounts Chem. Res.*, **1**, 1299 (1968).

(8) C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *J. Amer. Chem. Soc.*, **88**, 536 (1966).

(9) An *ionic* cyclization of 1 *via* catalysis by tri-*n*-butyltin bromide is improbable (it did not occur at 40°). Indeed, such a complication has been sought and found absent in a sensitive substrate system by Kuivila.[7]

(10) A "concerted cyclization" of 1 directly to 3 has not been included. Though Walling, *et al.*,[8] suggested such a step, Struble, *et al.*,[4] found it to be absent in work somewhat related to the present.

(11) F. H. Seubold, Jr., *J. Amer. Chem. Soc.*, **75**, 2532 (1953).

(12) D. J. Carlsson and K. U. Ingold, *ibid.*, **90**, 1055 (1968). We used a frequency factor of 10^{11} M^{-1} sec^{-1} to calculate the energy of activation, E_{act}.

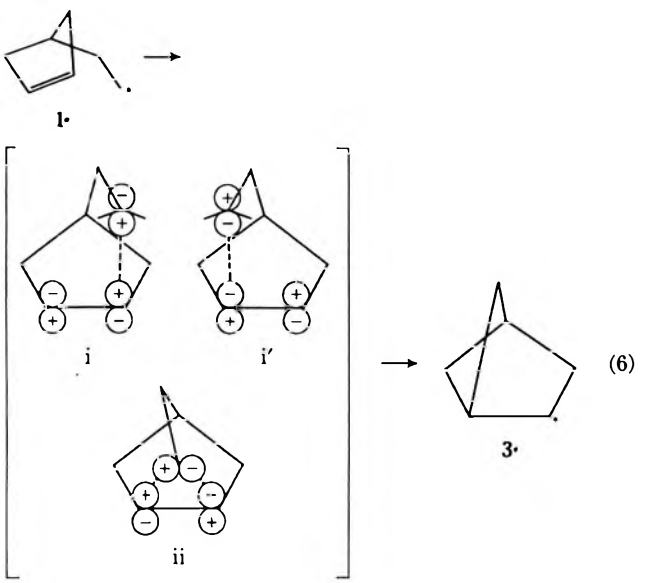
(13) Modeled after the calculation of Hill, *et al.*, for the anionic case.[6] However, the radical cyclization involves formation of a 2° radical, estimated as *ca.* 3.5 kcal mol^{-1} *more* stable than a 1° radical; so instead of $\Delta H = -2.8$ kcal mol^{-1} as in the carbanion,[6] we obtain a value of -8.8 kcal mol^{-1} for the radical. Otherwise, the treatment is the same.

(14) *Cf.* D. I. Davies and S. J. Cristol, "Advances in Free-Radical Chemistry," Vol. I, G. H. Williams, Ed., Elek-Academic Press, London, 1965, Chapter 5.

(15) It should be mentioned that radicals do not always cyclize. Certain strained radicals undergo ring opening [J. W. Wilt, L. L. Maravetz, and J. F. Zawadzki, *J. Org. Chem.*, **31**, 3018 (1966)], or fail to close [N. O. Brace, *ibid.*, **32**, 2711 (1967)].

(16) *Cf.* W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, pp 266–267 and references therein.

four electrons, a linear transition state is favored. One may view the *cationic* and *radical* cyclization of 2-(Δ³-



(6)

cyclcpentenyl)ethyl substrates as examples of the first cases, while the absence of cyclization in the *anionic* instance illustrates the last, as a linear arrangement of the three centers involved is sterically impossible.

Experimental Section

Melting and boiling points are uncorrected. Combustion analyses were performed by the microanalytical laboratories of the Universal Oil Products Co., Des Plaines, Ill. Gas–liquid partition chromatography (glpc) was carried out on F & M Model 720 and Varian Autoprep A-700 instruments. Infrared, nmr and mass spectra were determined on Beckman IR-5A, Varian A-60A and Consolidated Engineering Type 21-103C instruments.

3-Cyclopentene-1-carboxylic Acid.—The acid was prepared from diethyl 2-vinylcyclopropane-1,1-dicarboxylate by the method of Schmid and Wolkoff:[17] bp 75–77° (2.2 mm) [lit.[18] bp 83–85° (2 mm)]; δ^{neat} 12.13 s (COOH), 5.64 s (-CH=CH-), 3.1 m (>CH-), 2.7 distorted d (-CH_2-); λ^{neat} 3.0–4.2, 5.9 (COOH), 6.2, 14.5 (-CH=CH-).

Δ³-Cyclopentenylcarbinol.—The above acid was reduced to the oily carbinol with lithium aluminum hydride[19] in 95% crude yield: δ^{neat} 5.61 s (-CH=CH-), 5.13 t (-OH, slow exchange), 3.44 m (-CH_2OH), 2.2-2.0 m (other H's); λ^{neat} 3.0, 9.3, 9.6 (-CH_2OH), 3.3, 6.2, 14.9 (-CH=CH-). The crude carbinol was converted to the **tosylate** in the usual way with tosyl chloride in pyridine: 90%; mp 30–31.5°; λ^{neat} 7.35, 8.4, 8.5 (-OSO_2-).

Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 61.70; H, 6.36.

Δ³-Cyclopentenylacetonitrile.—The tosylate above (107 g) was refluxed for 16 hr in 90% aqueous ethanol with potassium cyanide (53.6 g). The material was poured into water and extracted with ether. Upon processing the ether extracts, the nitrile was obtained as a sweet-smelling oil: 38.1 g, 86%; bp 91–93° (30 mm); $n^{20}D$ 1.4988; d^{20}_4 0.9453; δ^{neat} 5.65 s (-CH=CH-), 2.8–1.7 m (all other H's); λ^{neat} 4.45 (CN).

Anal. Calcd for C_7H_9N: C, 78.46; H, 8.46. Found: C, 78.40; H, 8.53.

Δ³-Cyclopentenylacetic Acid.—The nitrile was hydrolyzed to this acid as described for a related case[2a] with alcoholic potassium hydroxide. The crude acid was used directly in the next step. Acid-catalyzed alcoholysis of the nitrile to the ethyl ester caused partial isomerization of the Δ³ double bond to the Δ² position and is not recommended.

2-(Δ³-Cyclopentenyl)ethanol.—Reduction of the above acid to the alcohol was achieved with lithium aluminum hydride in the usual way: 80%; bp 85–87° (15 mm); δ^{neat} 5.62 s (-CH=CH-), 4.9 s (-OH), 3.58 t (-CH_2CH_2OH), 2.4–1.7 m (other H's); λ^{neat} 3.0, 9.4 (-CH_2OH), 3.3, 6.2, 14.5 (-CH=CH-); lit.[2c] bp 82–85° (15 mm). The **tosylate** was obtained from the alcohol, tosyl chloride, and pyridine as a crude oil. Analysis by nmr indicated a purity of 89%, the remainder being pyridine. By this method Bartlett, *et al.*, obtained a crude tosylate of 88.7% purity.[2c]

2-(Δ³-Cyclopentenyl)ethyl Bromide (1).—Dry acetone was distilled from potassium permanganate and potassium carbonate. The above tosylate (38.3 g, 0.144 mol) and lithium bromide (36 g) were refluxed in this acetone (1400 ml) protected from moisture. Magnetic stirring prevented serious bumping. The acetone was removed on a rotary evaporator and the residual oil was taken up in ether. The ether material was washed well with water and brine and dried. Distillation afforded **1** as a colorless oil that was best stored over anhydrous potassium carbonate: 16.8 g, 67%; bp 71–72° (15 mm); $n^{20}D$ 1.4988; d^{20}_4 1.3066; δ^{neat} 5.63 s (-CH=CH-), 3.30 t (-CH_2CH_2Br), 2.7–1.7 m (other H's); λ^{neat} 3.3, 3.4, 6.2, 6.9, 7.4, 7.9, 8.2, 14.5; lit.[6] for less pure material, bp 68–70° (15 mm), $n^{23}D$ 1.4967, essentially same spectra. Analysis by glpc, ir, and nmr indicated no *exo*-2-norbornyl bromide in our sample.

Anal. Calcd for $C_7H_{11}Br$: C, 48.02; H, 6.33. Found: C, 47.91; H, 6.44.

4-Ethylcyclopentene (2).—2-(Δ³-Cyclopentenyl)ethyl tosylate was reduced to **2** with lithium aluminum hydride in ether under reflux for 2 days. The hydrocarbon was isolated by preparative glpc using 15% Carbowax 20M on Chromosorb A, 5 ft × ⅜ in, 120° (rearrangement occurred >150°): δ^{neat} 5.58 s (-CH=CH-), 2.2 m (other ring H's), 1.4 broad q further split (-CH_2CH_3), 0.9 distorted t (-CH_2CH_3, the spectrum illustrates virtual coupling); λ^{neat} 3.26, 3.51, 6.2, 6.85, 7.25, 10.75, 14.5, *inter alia* (identical with that published[20]).

Norbornane (3).—Norbornadiene (freshly distilled) was hydrogenated over palladium on charcoal at 50 psig to produce **3**. The nmr spectrum was free from olefinic contamination and the mass spectrum agreed with a published spectrum.[21]

Reactions of 1 with Tri-*n*-butyltin Hydride.—Tri-*n*-butyltin hydride [BTH, bp 73–75° (1 mm)] was prepared as reported.[22] Azobisisobutyronitrile (AIBN) was recrystallized from methanol, mp 100–102°. Di-*t*-butyl peroxide (DTBP) was freshly distilled, bp 51° (90 mm). Solutions of **1**, BTH, initiator (AIBN or DTBP) were made in benzene in a 30:10:1 ratio in the concentrations given in Table I. The benzene was distilled from sodium spheres. The solutions in ampoules were degassed by four freeze–thaw cycles and sealed. After a heating period, the contents were analyzed by glpc (Apieson L, 50–55°). The reaction at 40° (AIBN used) required 48 hr to show the desired conversion to products (10–20%), while at 93° (AIBN again used) 20 hr was sufficient. The study at 130° (DTBP used) needed only 15 hr. The composition of the product (**2** + **3**, no other products) was determined by glpc using calibration data from known mixtures. A larger scale run at 130° allowed the isolation of **3** as a pure product, identical *via* ir, nmr, and mass spectra and glpc behavior with an authentic sample. Several runs were made at each temperature and concentration. The data at 93 and 130° were closely duplicable (±1%), whereas at 40° the production of **3** was always just in trace amounts. Attempts to determine such small amounts quantitatively were not made.

Registry No.—3-Cyclopentene-1-carboxylic acid, 7686-77-3; Δ³-cyclopentenylcarbinol, 25125-21-7; Δ³-

(17) G. H. Schmid and A. W. Wolkoff, *J. Org. Chem.*, **32**, 254 (1967). This method involves, in part, the pyrolytic rearrangement of the cyclopropane diester at 400–425° to Δ³-cyclopentene-1,1-dicarboxylic ester. We found at 425–460° that the cyclopentene product was accompanied by some diethyl 2-butenylidenemalonate (15%). Details of this aspect of the work are available upon request.

(18) K. C. Murdock and R. B. Angier, *ibid.*, **27**, 2395 (1962).

(19) J. Meinwald, P. G. Gassman, and J. K. Crandall, *ibid.*, **27**, 3366 (1962).

(20) S. Pinchas, J. Shabtai, J. Herling, and E. Gil-Av, *J. Inst. Petrol.*, London, **45**, 311 (1959).

(21) American Petroleum Institute, Project 44, "Mass Spectral Data," Vol V, Serial No. 1466.

(22) H. G. Kuivila and O. F. Beumel, *J. Amer. Chem. Soc.*, **83**, 1246 (1961).

cyclopentenylcarbinol tosylate, 25125-22-8; Δ^3-cyclopentenylacetonitrile, 21860-24-2; 2-(Δ^3-cyclopentenyl)-ethanol, 766-01-8; **1**, 25125-25-1; **2**, 3742-38-9; **3**, 279-23-2; tri-*n*-butyltin hydride, 688-73-3.

Acknowledgment.—We thank the staffs of the microanalytical and spectral laboratories of the Universal Oil Products Co. for their cooperation and technical assistance.

Notes

Nitrogen-15 Magnetic Resonance Spectroscopy. X. Angular Dependence of Vicinal ^{15}N–H Coupling Constants in Amino Acids[1,2]

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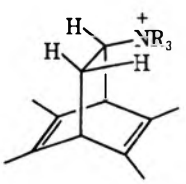
In contrast to the extensive investigations of the dependence of vicinal proton–proton and proton–fluorine coupling constants on dihedral angle, relatively little is known about the angular dependence of vicinal proton–nitrogen couplings in saturated systems. The principal reasons for this are experimental difficulties associated with the quadrupole-induced relaxation of ^{14}N and the relatively small magnitudes of ^{14}N–H coupling constants. However, Terui, Aono, and Tori[3] have recently demonstrated a geometrical dependence of the vicinal ^{14}N–H coupling in compounds of types **1** and **2** for dihedral angles of 0, 60, and 120°. More



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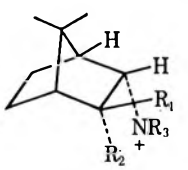
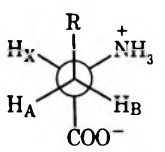


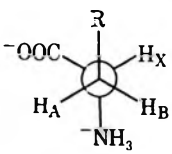
2

recently, Bothner-By and Cox[4] have reported values of *gauche* and *trans* ^{14}N–H coupling constants derived from aliphatic isocyanides, which agree well with those determined by Terui and coworkers.

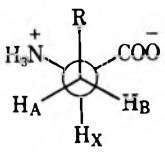
In connection with other studies, we have determined the proton magnetic resonance (pmr) chemical shifts and coupling constants for a series of ^{15}N-enriched amino acids. The H–C–C–H couplings in these spectra have been used to estimate the populations of the staggered rotational isomers **3a**–**3c**[5–9] and these, in conjunction with the N–C–C–H couplings, have been used to estimate the geometrical dependence of the vicinal N–H couplings. These couplings are much easier to measure with ^{15}N because ^{15}N ($I = {}^1/_2$) has no quadrupole moment and a slightly larger magnetogyric ratio than ^{14}N (see Figure 1).



3a



3b



3c

If we denote the fractional populations of **3a**–**c** by p_a, p_b, and p_c, respectively, and *trans* and *gauche* proton–proton coupling constants by J_t^H, J_g^H, respectively, the observed coupling constants are given by eq 1 and 2. With the knowledge that $p_a + p_b + p_c = 1$, the populations are given by

$$J_{BX} = p_a J_t^H + (p_b + p_c) J_g^H \quad (1)$$

$$J_{AX} = (p_a + p_c) J_g^H + p_b J_t^H \quad (2)$$

$$p_a = \frac{J_{BX} - J_g^H}{J_t^H - J_g^H} \quad (3)$$

$$p_b = \frac{J_{AX} - J_g^H}{J_t^H - J_g^H} \quad (4)$$

$$p_c = 1 - p_a - p_b \quad (5)$$

From eq 6 and 7, the *trans* and *gauche* vicinal ^{15}N–H

$$J_{NB} = (p_a + p_b) J_g^N + p_c J_t^N \quad (6)$$

$$J_{NA} = p_a J_t^N + p_c) J_g^N \quad (7)$$

$$J_g^N = \frac{p_c J_{NA} - p_a J_{NB}}{p_c - p_a} \quad (8)$$

$$J_t^N = \frac{J_{NB}(1 - p_a) - J_{NA}(p_a + p_b)}{p_c - p_a} \quad (9)$$

coupling constants are then given by eq 8 and 9. Evaluation of these expressions requires a knowledge of J_t^H and J_g^H. Pachler[5] has suggested 13.6 and 2.6 Hz, respectively, on the basis of a variety of experiments. These values have been discussed and supported by Cavanaugh[7] and will be used in the subsequent discussion.

The experimental data on which the calculations are based are given in Table I. Chemical shifts and coupling constants were assigned on the assumption that

(1) Part IX: W. Bremser, J. I. Kroschwitz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 6189 (1969).

(2) Supported by the Public Health Service, Grant No. 11072, from the Division of General Medical Sciences and by the National Science Foundation.

(3) Y. Terui, K. Aono, and K. Tori, *J. Amer. Chem. Soc.*, **90**, 1069 (1968).

(4) A. A. Bothner-By and R. H. Cox, *J. Phys. Chem.*, **73**, 1830 (1969).

(5) K. G. R. Pachler, *Spectrochim. Acta*, **19**, 2085 (1963); **20**, 581 (1964).

(6) H. Ogura, Y. Arata, and S. Fujiwara, *J. Mol. Spectrosc.*, **23**, 76 (1967).

(7) J. R. Cavanaugh, *J. Amer. Chem. Soc.*, **89**, 1558 (1967); **90**, 4533 (1968).

(8) F. Taddei and L. Pratt, *J. Chem. Soc.*, 1553 (1963).

(9) R. B. Martin and R. Mathur, *J. Amer. Chem. Soc.*, **87**, 1065 (1965).

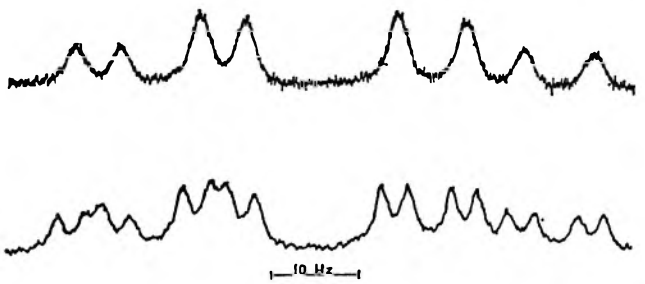


Figure 1.—Methylene region of phenylalanine. Upper trace is from the ordinary ^{14}N material, while the lower trace corresponds to the ^{15}N-labeled material. The spectra were measured at or near the isoelectric points and at different power and gain settings.

TABLE I

PROTON–PROTON AND PROTON–NITROGEN COUPLING CONSTANTS OF AMINO ACIDS[a]

Amino acid	Concn, M	J_{AX}[b]	J_{BX}[b]	J_{NA}[b]	J_{NB}[b]
Alanine (**3**, R = H)	0.43	7.0[c]		3.1[d]	
Phenylalanine (**3**, R = C_6H_5)	0.08	4.7[c]	7.9[c]	3.4[d]	2.9[d]
Aspartic acid (**3**, R = COOH)	0.05	3.1[d]	8.1[d]	3.0[e]	3.0[e]

[a] Measured at ambient probe temperatures, ~35° for alanine, ~19° for phenylalanine and aspartic acid. [b] In hertz. [c] ±0.1. [d] ±0.2. [e] ±0.3

rotamer **3a**, with the *trans* arrangement of the large R and COO^- groups, is predominant.[5,7] In accord with the above equations, the rotational isomer populations for phenylalanine are $p_a = 0.48$, $p_b = 0.19$, and $p_c = 0.33$ from which we can derive the *gauche* and *trans* ^{15}N–H couplings as $J_g^N = 1.8 \pm 0.8$ Hz and $J_t^N = 5.1 = 1.2$ Hz. The large probable errors are a consequence of the small difference between p_a and p_c.

Support for the derived values of J_g^N and J_t^N can be obtained in two ways. (1) Because alanine (**3**, R = H) has no preferred staggered conformation, the measured vicinal ^{15}N–H coupling constant must be a weighted average of the *trans* and *gauche* coupling constants, namely

$$J_{NH,vic} = \frac{1}{3}(2J_g^N + J_t^N) \qquad (10)$$

Substitution of the above values gives $J_{NH,vic} = 2.9$ Hz, in excellent agreement with the experimental value of 3.1 Hz.[10] (2) Using eq 3–5, the relative conformational populations of aspartic acid are $p_a = 0.50$, $p_b = 0.05$, and $p_c = 0.45$. These, in conjunction with equations 6–7, give calculated values of J_{NA} and J_{NB} as 3.5 ± 0.7 and 3.3 ± 1.5 Hz, which are in satisfactory agreement with the measured values.

The above treatment assumes that **3a** is the dominant conformation. If this is not assumed, and the assignments are reversed, then the alternative values of $J_g^N = 2.2$ Hz and $J_t^N = 5.8$ Hz result, which are within the probable error of the values derived above. Using these, a reasonable N–H coupling constant is derived for alanine, and values within the error limits of those given above are obtained for aspartic acid. Similarly, reversal of the aspartic acid assignments allows calculation of values for J_{NA} and J_{NB} whose error limits span the experimental value. Thus, the particular assignment of the amino acid chemical shifts is not critical to the derivation of J_t^N and J_g^N.

(10) The corresponding relationship should hold for the vicinal proton–proton coupling constant, but substitution for J_t^H and J_g^H gives 6.27 Hz,[4] compared with the experimental value of 7.0 Hz (Table I).

TABLE II

ANGULAR DEPENDENCE OF VICINAL NITROGEN-PROTON COUPLING CONSTANTS

Angle, deg	J_{NH},[a] Hz	J_{NH},[b] Hz	J_{NH},[c] Hz
0	1.9, 3.8	4.3	
60	<0.4	0.3, 1.0	1.8
120	<0.4, 1.1		
180		6.9, 8.7, 9.7	5.1

[a] Reference 3. [b] Reference 4. [c] This work.

In Table II, J_t^N and J_g^N are compared with those already reported.[11] Although the numerical agreement is far from perfect, it is perhaps better than one might expect, given the large differences in the structures of the compounds from which the values are derived. In any case, the trends are such that, if we assume all of the J_{NH} values have the same sign, the couplings define a fairly shallow and somewhat skewed Karplus-type correlation between dihedral angle and coupling constant. The minimum in the curve is uncertain but appears to be between 80 and 120°.

Experimental Section

Enriched alanine and phenylalanine were obtained from Bio-Rad Laboratories, while the aspartic acid was a product of Merck Sharpe and Dohme of Canada. Spectra were taken at ambient probe temperatures on Varian HA-60, A56/60, and HR-220[12] spectrometers. Chemical shifts were measured by direct counting of the sweep oscillator frequency (for the HA-60) or by the usual audio side-band calibration method (for the A56/60 and HR-220 spectrometers).

Registry No.—**3** (R = H), 56-41-7; **3** (R = Ph), 63-91-2; **3** (R = CO_2H), 56-84-8.

(11) The reported values for ^{14}N were corrected by $\gamma^{14}N/\gamma^{15}N = 0.713$ for this purpose.

(12) The HR-220 was purchased with the aid of National Science Foundation Grant No. GP 8450.

Charge-Transfer Energies of Benzylic Compounds with Tetracyanoethylene. A Convenient Method to Estimate the σ^* Values

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Received December 29, 1969

Much literature on the charge-transfer complex has arisen in the past decade both from experimental and theoretical point of view.[2] A simple molecular orbital treatment based on the perturbation theory has been applied successfully to the charge-transfer spectra of alternant and nonalternant hydrocarbons,[3] where the

(1) Department of Chemistry, Faculty of Science, Tohoku University, Katahira-cho, Sendai 980, Japan.

(2) G. Briegleb, "Elektronen-Donator-Acceptor-Komplexe," Springer-Verlag, Berlin, 1961.

(3) M. J. S. Dewar and A. R. Lepley, *J. Amer. Chem. Soc.*, **83**, 4560 (1961); A. R. Lepley, *ibid.*, **84**, 3577 (1962); K. Fukui, A. Imamura, T. Yonezawa, and C. Nagata, *Bull. Chem. Soc. Jap.*, **34**, 1076 (1961); **35**, 33 (1962).

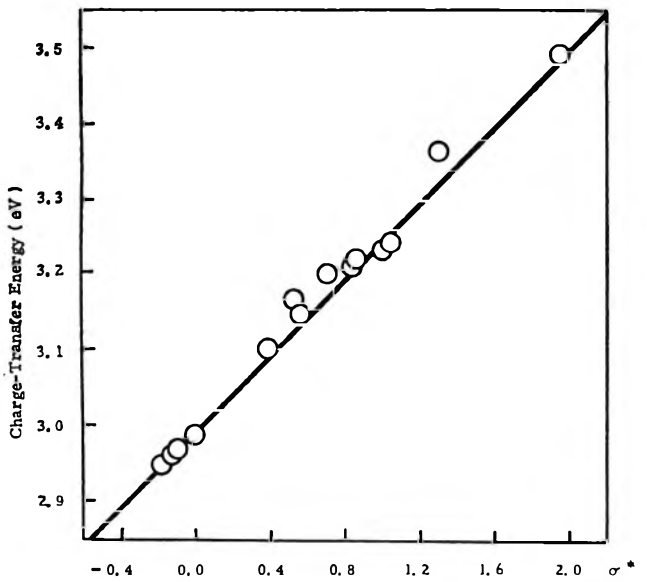

Figure 1.—Relationship between charge-transfer energies of $PhCH_2X$ and σ^* of CH_2X.

energy required for the charge-transfer is simply related to the energy of the electronic transition from the highest occupied molecular orbital of the donor hydrocarbons into the lowest unoccupied molecular orbital of an interacting acceptor molecule.

Now a number of charge-transfer spectra of π complexes of benzylic compounds have been measured with tetracyanoethylene (TCNE) in dichloromethane at an ambient temperature, the results being listed in Table I.

TABLE I
CHARGE-TRANSFER ENERGIES OF BENZYLIC COMPOUNDS WITH TETRACYANOETHYLENE

Benzylic compd, XCH_2Ph	Registry no.	λ_{max}^{CT}, nm	E_{CT}, eV	$\sigma^*_{XCH_2}$
(Cl_2CHPh)	98-87-3	355	3.49	1.94
$NCCH_2Ph$	140-29-4	369	3.36	1.30
$ClCH_2Ph$	100-44-7	383	3.24	1.05
$BrCH_2Ph$	100-39-0	384	3.23	1.00
$CH_3CO_2CH_2Ph$	140-11-4	385	3.22	0.86
$PhOCH_2Ph$	946-80-5	390	3.18	0.85
$C_2H_5O_2CCH_2Ph$	101-97-3	388	3.20	0.71
$HOCH_2Ph$	100-51-6	393	3.15	0.555
CH_3OCH_2Ph	538-86-3	390	3.17	0.52
$ClCH_2CH_2Ph$	622-24-2	400	3.10	0.385
CH_3Ph	108-88-3	415	2.99	0
CH_3CH_2Ph	100-41-4	417	2.97	−0.1
n-C_4H_9Ph	104-51-8	419	2.96	−0.13
i-C_3H_7Ph	99-82-8	420	2.95	−0.19

The values of charge-transfer energies (E_{CT} in eV) are plotted against σ^* as shown in Figure 1. A good linear relationship was obtained.

$$E_{CT}\ (eV) = 0.254\sigma^* + 2.99_0 \quad (r = 0.991)$$

Lepley[4] has demonstrated that the charge-transfer spectra of the π complexes of a number of methyl-substituted benzenes and naphthalenes with TCNE can be reasonably explained in terms of the first-order perturbation theory using only inductive effect models.[5] Therefore, in simple benzylic compounds, $PhCH_2X$, the charge-transfer energies can be related to parameters of inductive effect of XCH_2, *i.e.*, $\sigma^*_{XCH_2}$,[6] since in simple LCAO of $PhCH_2X$ only the atomic orbital at the point of XCH_2 attachment should be effected appreciably.

The present findings demonstrate not only the validity of using the inductive effect models to explain the charge-transfer spectra of simple hydrocarbons, but also potential utility of the relationship to evaluate the σ^* value of XCH_2 group.

It should be noted, however, that there are apparent exceptions to the present relationship, for example, benzyltrimethylsilane ($\sigma^*_{Me_3SiCH_2} = -0.26$) afforded two well-resolved charge-transfer maxima at 491 and 415 nm as reported recently by Bock and Alt,[7] but the data deviated considerably from the above equation.

Recently, Traylor, *et al.*,[8] have measured charge-transfer absorptions in complexes of TCNE with substituted benzenes in dichloromethane. They have treated the data in a somewhat different manner, namely, in connection with the ability of substituents to stabilize carbonium ions The charge-transfer frequencies for the compounds, C_6H_5Y (Y = Me, PhCONH, MeO, MeCONH), correlate satisfactorily, although not perfectly, with σ_p^+. They have also shown that the benzyl–metal bonds such as in $PhCH_2SiMe_3$ and $PhCH_2HgCH_2Ph$ are highly hyperconjugated if a positive charge is in the ring and that the charge-transfer frequencies for these compounds are also correlated with σ_p^+.

However, the ionization energies or charge-transfer frequencies may be treated by the Hammett equation only in the case that the substituent causes rather a small perturbation on the benzene ring.[8] Actually, Traylor has measured the charge-transfer frequencies of various benzyl-X (X not a hyperconjugative) with TCNE and has plotted them against σ_I.[9]

In summary, the relationship found in the present investigation will be useful to estimate σ^* values in the range of $-0.2 \sim +2.0$. Applications of this relationship will be reported later.

Experimental Section

Materials.—Benzylic compounds purchased or prepared by known procedures were purified by distillation, purities being checked by glpc. TCNE was obtained from Eastman Organic Chemicals and was used without further purification.

Spectra.—Charge-transfer spectra were run on a Shimadzu Model SV-50A automatic recording spectrophotometer using 10-mm quartz cell. Dichloromethane was used as the solvent throughout the experiment, concentrations of TCNE and benzylic compounds being kept at 10^{-4}–10^{-3} and 10^{-2}–10^{-1} mol/l., respectively. The solutions were made up and mixed immediately before measurement. These solutions decolorized fairly rapidly, but were stable enough to record the charge-transfer maxima two or three times.

(4) A. R. Lepley, *J. Amer. Chem. Soc.*, **86**, 2545 (1964).

(5) See, for more sophisticated treatment, R. L. Flurry, Jr., *J. Phys. Chem.*, **69**, 1927 (1965); S. Iwata, J. Tanaka, and S. Nagakura, *J. Amer. Chem. Soc.*, **88**, 894 (1966); A. R. Lepley and C. C. Thompson, Jr., *ibid.*, **89**, 5523 (1967).

(6) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, Chapter 13.

(7) H. Bock and H. Alt, *Chem. Commun.*, 1299 (1967); *Angew. Chem.*, **79**, 934 (1967).

(8) W. Hanstein, H. J. Berwin, and T. G. Traylor, *J. Amer. Chem. Soc.*, **92**, 829 (1970).

(9) T. G. Traylor, private communication.

Registry No.—Tetracyanoethylene, 670-54-2.

Acknowledgment.—The author is grateful to Professor T. G. Traylor for making his results available prior to publication and for helpful discussions.

The Sodium Borohydride Reductions of Indolylethylpyridinium Bromides. Hexahydroindoloquinolizines

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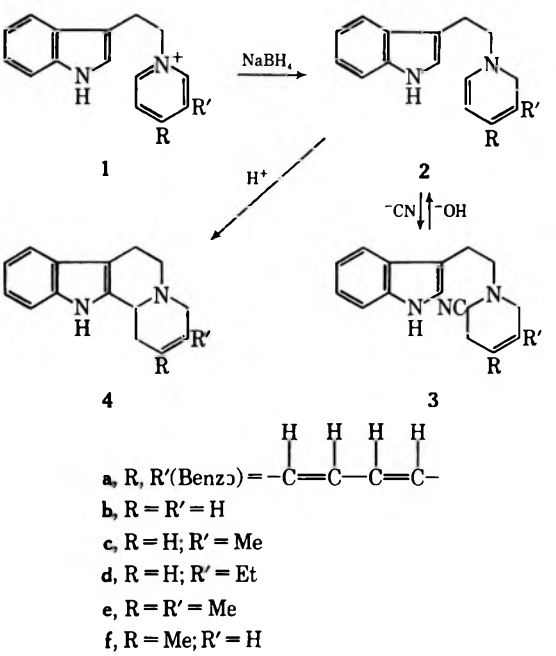
Sodium borohydride under ordinary conditions has not proved useful for the reduction of 1-(2-indol-3-ylethyl)pyridinium and the corresponding isoquinolinium salts to the dihydro bases **2**, intermediates for the synthesis of the quinolizines **4**.[1-4] The reduction to the tetrahydro bases which characterized this reagent was observed to a lesser extent with lithium aluminum hydride[1-5] and with lithium tri-*t*-butoxyaluminum hydride.[3] The results presented in this note show that control over the sodium borohydride reduction can be easily gained by using the alklai method of Panouse[6] together with the rapid removal of products from the reaction site. In addition, conversion of the dihydropyridines into nitriles in the reaction medium proved to be convenient and was usually desirable.[7a]

The advantages of using a nitrile in a sequence involving a 1,2-dihydropyridine lie in its stability relative to the parent diene and in the ease with which the nitrile reverts to the diene under basic and acidic conditions. Its availability, however, may be limited by the alkalinity of the parent sodium cyanide reduction system which may in itself be high enough to make the **2** ⇄ **3** equilibrium favor the diene. Lowering the alkalinity of the cyanide solution shifts the equilibrium toward the nitrile, but whether there is an accompanying increase in liability to further reduction is not presently known. Previous investigations have shown that annelations of the dienes require acid conditions, and in the present work the nitriles readily lost hydrogen cyanide in hot acid with closure to the quinolizine salts. Much milder conditions effect this ring closure when the dihydropyridine system is involved, so that the yield of quinolizine from a reduction mixture containing both **2** and **3** can in itself give no information on the relative amounts of the precursors.

A constant factor in all reductions and one of great importance is the two-phase liquid mixture of water, methanol, and ether which provided for a rapid separation of the initial reduction products from the foaming reaction mixture. By this means alone and without additional alkali a 66% yield of **2a** was obtained; in the presence of sodium hydroxide the recovery of this base rose to 89%. The dihydro base **2a** was also the main product from reductions in the more concentrated sodium cyanide solutions, and only in a moderately basic cyanide solution (partial neutralization with acid) did the nitrile form in appreciable amount in the reaction mixture. Not unexpectedly, **2a** was readily converted into **3a** (94%) in a similar cyanide solution. In contrast with the results obtained with the isoquinolinium salt, the water–methanol–ether mixture did not prevent reduction of the pyridinium bromide **1b** into its tetrahydro base in 78% yield; no quinolizine was obtained. The reduction of **1b** in sodium hydroxide followed by acid ring closure gave the hydrochloride of **4b** in 40% yield, and this was increased to 50% by the cyanide technique. Here noncrystalline products precluded assessment of the **2** ⇄ **3** interchange, but the ir absorption spectra indicated that this mixture was present in the crude oil.



a, R, R′(Benzo) = –C=C–C=C–
b, R = R′ = H
c, R = H; R′ = Me
d, R = H; R′ = Et
e, R = R′ = Me
f, R = Me; R′ = H

Among the variables to which little attention was given, but which made necessary a standardization of the synthetic procedure, are two which deserve special mention. The first of these is the alcohol used to dilute the aqueous solutions. Whether its contribution to the product yield stems from its role as a solvent or whether it also functions as a moderating nucleophile is a matter of conjecture. The second is the manner in which the acid annelation is conducted. Minor variations in solvent and acid sometimes had a marked effect on the yield of quinolizine salt. No attempt was made to identify a cause, but care was taken to duplicate conditions where comparisons were made.

Acid-induced elimination of hydrogen cyanide from related cyanotetrahydropyridines has been observed to be followed by a shift of the double bond into conjugation with the azomethine linkage. This isomerization has proved useful in controlling steric requirements of

(1) K. T. Potts and R. Robinson, *J. Chem. Soc.*, 2675 (1955).
(2) (a) R. C. Elderfield, B. Fischer, and J. M. Lagowski *J. Org. Chem.*, **22**, 1376 (1957); (b) R. C. Elderfield and B. A. Fischer, *ibid.*, **23**, 949 (1958).
(3) A. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Amer. Chem. Soc.*, **84**, 3732 (1962).
(4) J. W. Huffman, *ibid.*, **80**, 5193 (1958).
(5) (a) D. R. Liljegren and K. T. Potts, *J. Org. Chem.*, **27**, 377 (1962); (b) K. T. Potts and D. R. Liljegren, *ibid.*, **28**, 3066 (1963).
(6) (a) J. J. Panouse, *Bull. Soc. Chim. Fr., D*, 60 (1953); (b) J. J. Panouse, Thèse de Doctorate ès Sciences, Paris, 1952.
(7) (a) E. M. Fry, *J. Org. Chem.*, **29**, 1647 (1964); (b) E. M. Fry, *ibid.*, **28**, 1869 (1963).

substituted methanobenzazocines (benzomorphans)[7b,8] and might reasonably by expected here, but nmr examination of the suitably substituted examples **4c–e** showed the double bond to be in its original position. Additional evidence for the position of the double bond was provided in all cases by a strong band in the mass spectrum for the dihydro-β-carboline ion, *m/e* 170, resulting from a reverse Diels–Alder reaction.

Experimental Section

Analyses and mass and nmr spectra were performed by the Analytical Services Section of this laboratory, William C. Alford, Chief. Uv spectra were obtained by a Beckman DB-G grating spectrophotometer; ir spectra by a Perkin-Elmer Infracord Model 137B; nmr spectra by a Varian 60-Mc spectrometer with tetramethylsilane internal standard, and mass spectra by a Hitachi Perkin-Elmer RMU-7 mass spectrometer. Melting points are uncorrected; when reported as "vac mp," melting points were taken in evacuated capillary tubes made from Kimble disposable pipets.

Pyridinium and isoquinolinium bromides (1) were made by heating a small excess of base with tryptophyl bromide at 50° for about 5 hr or by letting the mixture stand at room temperature for several days. The finely divided crystalline state used in the reductions was obtained by continuously scratching the test tube sides during the cooling of a hot concentrated solution. Yields are based on tryptophyl bromide.

2-(2-Indol-3-ylethyl)isoquinolinium bromide (**1a**) was obtained in 80% yield, mp 207–215°. After recrystallization from alcohol it melted at 215–217° (lit.[4] mp 211–212°).

1-(2-Indol-3-ylethyl)pyridinium bromide (**1b**) was obtained in a yield of 83% after recrystallization from aqueous alcohol, mp 230–232° (lit.[3] mp 231–233°).

3-Methyl-1-(2-indol-3-ylethyl)pyridinium bromide (**1c**) was recovered in 78% yield after recrystallization from alcohol. It melted at 204–206°.

Anal. Calcd for $C_{16}H_{17}BrN_2$: C, 60.57; H, 5.40; N, 8.83. Found: C, 60.66; H, 5.29; N, 8.96.

3-Ethyl-1-(2-indol-3-ylethyl)pyridinium bromide (**1d**) was obtained in 70% yield after recrystallization from methanol–acetone. It melted at 154–156° (lit.[3] mp 137–140°).

Anal. Calcd for $C_{17}H_{19}BrN_2$: C, 61.64; H, 5.79; Br, 24.12. Found: C, 61.35; H, 5.91; Br, 23.94.

3,4-Dimethyl-1-(2-indol-3-ylethyl)pyridinium bromide (**1e**) was obtained in 92% yield before purification. Recrystallized from water it sintered at 175°, resolidified, and melted at 220°. Recrystallized from alcohol it melted at 215–222°.

Anal. Calcd for $C_{17}H_{19}BrN_2$: C, 61.64; H, 5.78; N, 8.46. Found: C, 61.44; H, 5.98; N, 8.23.

4-Methyl-2(2-indol-3-ylethyl)pyridinium bromide (**1f**) was recovered in 88% yield, mp 197–200°. Recrystallized from alcohol it melted 199–201°.

Anal. Calcd for $C_{16}H_{17}BrN_2$: C, 60.57; H, 5.40; N, 8.83. Found: C, 60.58; H, 5.47; N, 8.65.

Reductions of 1b. A. In Methanol–Water. 1-(2-Indol-3-ylethyl)-1,2,5,6-tetrahydropyridine.—To a solution of 0.10 g of sodium borohydride in 1 ml of water was added 1 ml of methanol and 4 ml of ether. The addition of 0.40 g of **1b** gave a vigorously effervescing mixture which was stirred and intermittently cooled. The solid was consumed in about 10 min. The ether solution was separated and the crystalline product was recovered and converted to the picrate, 0.47 g (78%), mp 165–171°. After recrystallization from alcohol it melted at 173–175° (lit.[3] mp 173–174.5°).

Anal. Calcd for $C_{21}H_{21}N_5O_7$: C, 55.38; H, 4.65; N, 15.38. Found: C, 55.46; H, 4.90; N, 15.53.

Recovery of the base from the picrate with lithium hydroxide–ether gave material melting at 117–122°. The same base, mp 117–122°, was obtained in 35% yield by following the published procedure.[2a] After recrystallization from alcohol–petroleum ether, it melted at 119–123° (lit.[2a] mp 152–153°, similar melting points were reported in subsequent papers);[3,5b] mass spectrum M^+ 226; nmr ($CDCl_3$) ind-NH 8.4 (1 H), ind-α-H 7.0 (1 H), olefinic CH 5.8 ppm (2 H); uv spectrum in ethanol λ_{max} (log ε) 290.5 (3.69), 282 (3.74), 276 s (3.72), 229 (3.86); λ_{min} (log ε) 288 (3.66), 245 (3.14) [lit.[2a] λ_{max} (log ε) 291 (3.68), 283 (3.74), 275 s (3.71); λ_{min} (log ε) 288 (3.65), 244 (2.95)].

Anal. Calcd for $C_{15}H_{16}N_2$: C, 79.60; H, 8.02; N, 12.18. Found: C, 79.19; H, 8.16; N, 12.60.

In a duplicate experiment, a solution of the crude product in acid gave no **4b**.

B. In Methanol–Water–Sodium Hydroxide. 1,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine (**4b**).—To a solution of 30 mg of sodium borohydride in 0.5 ml of 2.1 *N* sodium hydroxide was added 0.5 ml of methanol and 2 ml of ether. The addition of 200 mg of **1b** resulted in a vigorous gas evolution and consumption of the solid was complete in 5 min. The product obtained from a sample of the ether solution showed a broad, strong band in the 6.1 μ region (diene) of the infrared. The ether solution was separated and extracted with 1 ml of 3 *N* hydrochloric acid. The yellow gum which formed began to yield crystalline material in 15 min, and after 1.5 hr the waxy solid was removed and triturated with alcohol to yield 68 mg (39.6%) of salt. Recrystallization from alcohol containing a drop of 1 *N* hydrochloric acid gave a product melting at 275–292°. In a duplicate run the ether solution was shaken with 1 ml of 3 *N* 95% ethanolic hydrochloric acid and the salt was obtained in only 23% yield.

Anal. Calcd for $C_{15}H_{17}ClN_2$: Cl, 13.60. Found: Cl, 13.40.

The salt was decomposed in sodium hydroxide containing a little alcohol and the base was recovered from ether. Recrystallized from ethanol it melted at 142–144° (lit.[3] mp 145–146°); picrate mp 187–190° (lit.[3] mp 184–187°).

Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; N, 7.19. Found: C, 80.17; H, 7.39.

C. In Methanol–Water–Sodium Cyanide. 1,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine Hydrochloride (**4b**).—Sodium borohydride, 30 mg, was dissolved in a solution of 0.20 g of sodium cyanide in 0.6 ml of water. To this was added 0.5 ml of methanol and 2 ml of ether. **1b**, 200 mg, was added and the foaming mixture was stirred until the salt disappeared in about 10 min. The ether solution was then separated and distilled to a small volume and the residual methanol was removed under reduced pressure. The crude product showed a nitrile band at 4.5 μ and the 6.1-μ absorption was less intense than that observed in the B experiment above. The oil was redissolved in a small volume of ether and triturated with 1 ml of 3 *N* hydrochloric acid. In an 80° bath the mixture lost ether and hydrogen cyanide (sodium picrate vapor test). Crystal formation began in about 10 min, and after 35 min the material was filtered and then triturated with alcohol for a recovery of 90 mg (52%). Identification with the above described salt **4b** hydrochloride was made by comparison of infrared spectra and by conversion to the base.

In another experiment, an attempted ring closure in a dilute alcohol solution of lower acidity gave a very poor result.

3-Methyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (**4c**).—The hydrochloride was obtained from **1c** in 53% yield using the amounts and procedure described for **1b** under procedure C above. Recrystallized from alcohol containing 1 *N* hydrochloric acid, it melted at 290–295°.

Anal. Calcd for $C_{16}H_{19}ClN_2$: Cl, 12.90. Found: Cl 12.6.

The salt was decomposed by aqueous sodium carbonate–alcohol and the base was recovered from ether. It was recrystallized from alcohol: vac mp 174–176°; mass spectrum *m/e* 238 (M^+) 170; nmr ($CDCl_3$) Me 1.7 (3 H), olefinic CH 5.5 ppm (1 H).

Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.21; H, 7.42; N, 12.11.

3-Ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (**4d**).—The hydrochloride was obtained in 49% yield by the cyanide method. The base melted at 147–148° (lit.[5b] mp 146–148°); mass spectrum *m/e* 252 (M^+) 170; nmr ethyl CH_3, triplet, 1.05 (3 H), olefinic CH 5.5 ppm (1 H).

6-Cyano-3,4-dimethyl-1-(2-indol-3-ylethyl)-1,2,5,6-tetrahydropyridine (**3e**) **Hydrochloride.**—**1e**, 200 mg, was reduced in the manner described for **1b** under the cyanide procedure C above. Approximately 1 hr was required for consumption of the solid. After separation, the ether solution was triturated with 0.2 ml of 3 *N* hydrochloric acid. The oil which formed crystallized in a few minutes. After decanting the ether, the product was washed with water to remove a little gum. It weighed 0.11 g (67.6%), mp 160° (gas).

Anal. Calcd for $C_{18}H_{22}ClN_3$: C, 68.45; H, 7.03; N, 13.30. Found: C, 68.55; H, 7.25; N, 12.91.

(8) R. L. Perry and N. F. Albertson, *J. Med. Chem.*, **10**, 1184 (1967).

The salt was decomposed in alcoholic sodium bicarbonate solution and the base was recovered as an oil from ether. Nmr spectrum ($CDCl_3$) showed ind-NH 8.2, *ind*-α-H 6.95 ppm.

2,3-Dimethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (4e).—**3e** hydrochloride, 0.43 g, suspended in 4.3 ml of 1 *N* hydrochloric acid was held on steam for 1 hr during which time hydrogen cyanide was evolved and cottony crystals replaced the original salt. The suspension was chilled and 0.35 g (89%) of salt was recovered. It was recrystallized from water, mp 295°.

Anal. Calcd for $C_{17}H_{21}ClN_2$: Cl, 12.28. Found: Cl, 12.25.

The salt was decomposed in sodium bicarbonate solution containing alcohol and the base was recovered from ether. Recrystallized from alcohol it had vac mp 192–193°, with a slight sinter at 93°; mass spectrum *m/e* 252 (M^+) 170; nmr ($CDCl_3$) Me 1.68 ppm (6 H).

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99. Found: C, 81.10; H, 7.73; loss on drying, 3.34.

6-Cyano-4-methyl-1-(2-indol-3-ylethyl)-1,2,5,6-tetrahydropyridine (3f).—**1f**, 200 mg, was reduced as described for **1b** under procedure C above. After a reaction time of 30 min, the ether was separated and distilled to a small volume, and the remaining solvent was removed under reduced pressure to yield crystalline material which was triturated with petroleum ether and filtered, 0.15 g, mp 93–120°. After several recrystallizations from alcohol, it melted at 128–130°.

Anal. Calcd for $C_{17}H_{19}N_3 \cdot {}^1/_2H_2O$: C, 74.42; H, 7.34; N, 15.32. Found: C, 74.19; H, 6.84; N, 15.62.

2-Methyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (4f).—The hydrochloride was obtained from a like preparation after the crude crystalline cyano product was converted in the usual manner. The salt weighed 0.112 g (65%) and darkened without melting at 310° (hot stage).

Anal. Calcd for $C_{16}H_{19}ClN_2$: Cl, 12.90. Found: Cl, 12.64.

The salt was decomposed in aqueous sodium hydroxide–alcohol and the base was recovered with ether. Recrystallized from *n*-hexane–ether it melted at 121–123° (gas). After heating at 80° under reduced pressure for 45 min to remove solvent, it melted at 149–151°; mass spectrum *m/e* 238 (M^+) 170.

Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.69; H, 7.73; N, 12.02.

Reductions of 1a. A. In Methanol–Water. 2-(2-Indol-3-ylethyl)-1,2-dihydroisoquinoline (2a).—A solution of 30 mg of sodium borohydride in 0.5 ml of water was mixed with 0.5 ml of methanol and 2.0 ml of ether. To this was added 200 mg of **1a** and the vigorously foaming mixture was stirred until the reaction ended in 3 min with exhaustion of the hydride. The ether layer was separated and 11 mg of **1a** was recovered. After concentration of the ether solution crystallization took place and 98 mg (66%) was recovered from a cold alcohol suspension, vac mp 136–144°. After recrystallization from alcohol it showed vac mp 148–151°; ir spectrum (Nujol) 6.18 (strong), 6.40 μ (medium); nmr spectrum ($CDCl_3$) ind-NH 7.8 (1 H), ind-α-H 6.9, olefinic CH, AB doublets (J = 7.8 Hz) 6.1 (1 H), 5.2 ppm (1 H); and uv spectrum (ethanol) λ_{max} (log ε) 334 (3.96), 291 (3.84), 283 (3.83), 276 sh (3.79), 229 (4.15); λ_{min} (log ε) 301 (3.70), 287 (3.81), 255 (3.63) [lit.[4] mp 100° for unpurified product; λ_{max} (log ε) 336 (3.83), 293 (3.85), 284 (3.88), 278 sh (3.87), 221 (4.69)].

Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61. Found: C, 83.34; H, 6.37.

2-(2-Indol-3-ylethyl)-1,2,3,4-tetrahydroisoquinoline.—The noncrystalline product from the alcohol wash was converted to a picrate, 40 mg (15%), mp 161–169°. Purified from alcohol it melted at 170–173° (lit.[4] mp 170–171°). It was converted to the base with lithium hydroxide and recovered from ether. After recrystallization from alcohol, it melted at 118–120° (lit.[4] mp 121–122°).

B. In Methanol–Water–Sodium Hydroxide. 2-(2-Indol-3-ylethyl)-1,2-dihydroisoquinoline (2a).—By the procedure detailed for **1b**, 200 mg of **1a** was subjected to reduction in methanolic sodium hydroxide. It was consumed in 2 min. The ether was distilled to a small volume and the residual solvent was removed under reduced pressure. The crystalline residue was filtered from cold alcohol, 129 mg (83%), vac mp 152–154°. A second crop of 10 mg brought the total recovery of **2a** to 89%.

C. In Methanol–Water–Sodium Cyanide. 3-Cyano-2-(2-indol-3-ylethyl)-1,2,3,4-tetrahydroisoquinoline (3a).—A. Sodium borohydride, 30 mg, was dissolved in a solution of 0.2 g of sodium cyanide in 0.3 ml of water. Methanol, 0.5 ml, was added and the solution was layered with 2 ml of ether. **1a**, 200 mg, was added and the effervescing mixture was stirred. Consumption of the salt was complete in 5 min. The product, 98 mg (63%) mp 137–146°, was recovered from the ether solution in the usual manner. Its identity as **2a** was established by means of an infrared spectrum. The alcoholic filtrate yielded 11 mg (6%) of the crystalline nitrile. B. When the reduction was run in a solution less concentrated in sodium cyanide (0.2 g of sodium cyanide, 0.5 ml of water, 0.5 ml of methanol) the same products were isolated in 50% and 24% yields, respectively. C. To an ice-cold partial solution of 0.2 g of sodium cyanide in 0.3 ml of water was carefully added 0.3 ml of 6 *N* hydrochloric acid. Sodium borohydride, 30 mg, was then dissolved in the still alkaline solution and this was followed by the addition of 0.5 ml of methanol and 2 ml of ether. Reduction of 200 mg of **1a** gave 110 mg (65%) of the nitrile, mp 94–106°. The noncrystalline residue yielded 42 mg (15%) of the picrate of 2-(2-indol-3-ylethyl)-1,2,3,4-tetrahydroisoquinoline. No **2a** could be isolated. D. **2a**, 77 mg, was stirred with a sodium cyanide–hydrogen cyanide solution made as above. The solid became gummy in 30 min and then resolidified on continued trituration. Recovery gave 80 mg (94%), mp 95–105°. Identity with the other nitrile samples was established by its ir (Nujol) spectrum. Recrystallization from alcohol gave a product melting at 108–110°.

Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.49; H, 6.33; N, 13.70.

The hydrochloride separated as finely divided crystals when the base was added to 3 *N* alcoholic (95%) hydrochloric acid.

Anal. Calcd for $C_{20}H_{20}ClN_3$: Cl, 10.48. Found: Cl, 10.83.

5,7,8,13,13b,14-Hexahydrobenzo[*g*]indolo[2,3-*a*]quinolizine (4a).—A. The hydrochloride from 60 mg of nitrile **3a** was obtained crystalline in 0.5 ml of 3 *N* alcoholic (95%) hydrochloric acid. The suspension was diluted with an equal volume of water and held on the steam bath for 5 min. The solid became less dense and the vapor was positive to the picrate test for hydrogen cyanide. After washing with alcohol 55 mg (89%) of salt was obtained. B. **2a**, 111 mg, was added portionwise with stirring to 2 ml of 2.4 *N* ethanolic (95%) hydrochloric acid to give a solution which began to deposit crystals in 5 min. Recovery after 1 hr gave 90 mg (71%) of the salt. Identity of material from the two sources was established by ir spectra (Nujol). The salt melted at 290° (lit.[1] mp 287–288°). C. Ether solutions containing mixtures of **2a** and **3a** (from sodium borohydride reductions in cyanide solutions) were extracted with 3 *N* aqueous hydrochloric acid to yield oils which crystallized to give the salt in 60–65% yields.

The base was recovered crystalline from ether–alcohol after decomposing the salt in sodium carbonate solution containing alcohol. It had vac mp 197–200°, air mp 192–195° (lit.[1] mp 188–189°); mass spectrum *m/e* 274 (M^+) 170.

Registry No.—Sodium borohydride, 16940-66-2; **1c**, 24716-23-2; **1d**, 24716-24-3; **1e**, 24716-25-4; **1f**, 24716-26-5; 1-(2-indol-3-ylethyl)-1,2,5,6-tetrahydropyridine, 24716-27-6; **2a**, 24716-28-7; **3a**, 24716-29-8; **3e**-HCl, 24716-30-1; **3f**, 24716-31-2; **4b** HCl, 24716-32-3; **4c**, 24716-33-4; **4c** HCl, 24716-34-5; **4e**, 24716-35-6; **4e** HCl, 24716-36-7; **4f**, 24716-37-8; **4f** HCl, 24716-38-9.

Biphenylene Insertion Products. Dibenzoselenophene and Diphenyldibenzostannole

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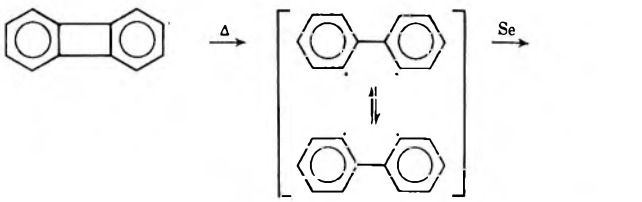
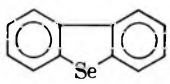
A conventional approach to the chemistry of biphenylene, involving synthesis and characterization of ring-substituted derivatives, has revealed a wealth of

detail about this hydrocarbon.[1-3] Until recently, a chemistry directly involving the central ring was thought not to exist.[4] The unique feature of this hydrocarbon, its strained four-membered ring, is only now receiving a full measure of attention.[4-8]

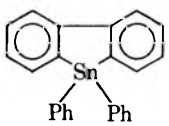
Some observations we made are especially germane to the chemistry of the inner ring. If selenium and biphenylene are refluxed together at *ca.* 275° for 22 hr, dibenzoselenophene (II) is formed (14% based on starting materials; *ca.* 75% recovery of biphenylene). Reaction for longer times leads to extensive tarring and decreased yields of dibenzoselenophene (II), apparently by its further reaction with the ring-opened diradical I.



I



II

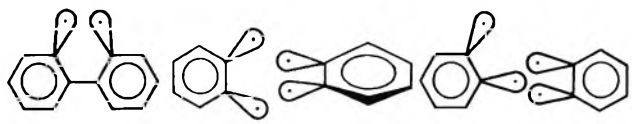


III

Reaction of $(Ph_2Sn)_5$[9] with biphenylene led to several new products in low yield. The quantity of material available did not permit isolation of the separate products, but thin layer chromatography showed a product with the same R_f value as authentic diphenyldibenzostannole (III)[9,10] upon elution with each of 13 different solvents. The mass spectrum of the product showed peaks attributable to III. This material is not present in the pyrolysis products of $(Ph_2Sn)_5$ or Ph_4Sn. Owing to lack of starting materials, optimum conditions for this reaction were not determined.

Biphenylene gave no insertion products upon pyrolysis with Te,[11] Ph_3P,[12] or SO_2 (1 atm), and most of the biphenylene was recovered. Insertion of SO_2 would have provided a route to dibenzothiophenes from biphenylenes (the direct route from elemental sulfur is closed; only black tar is obtained[4]).

Representation of the reactive intermediate as I is not intended to distinguish between VI, VII, and VIII. Unlike VI, the species represented by VII and VIII both allow a 1,8-disubstituted biphenylene to yield a 1,5-disubstituted dibenzoselenophene. Likewise, quenching VII or VIII could give a rearranged biphenylene. The observed fragmentation of I to produce benzyne[4] argues for the intervention of VII or VIII if only as higher energy intermediates.



VI VII VIII

Experimental Section

The booling point of biphenylene was determined to be 275 ± 5° by capillary microtechnique. Specified quantites of reagents in ordinary nmr tubes were heated at this temperature for the indicated times in an electrically heated aluminum block (Gallenkamp melting point apparatus).

Dibenzoselenophene (II).—Biphenylene (0.001 mol, 0.152 g) and selenium powder (0.200 g, 2.5-fold excess) were refluxed for 22 hr. The reaction mass was extracted with THF (0.148 g recovered, mp 105–110°) and examined by vpc, tlc, and nmr. Retention time, R_f values (ligroin, benzene), and nmr spectrum[13,14] were identical with those of authentic dibenzoselenophene. The product identification was confirmed by melting point and mixture melting point. The yield was 14% based on starting materials, and 75% biphenylene was recovered.

When a similar reaction was allowed to proceed for 65 hr, considerable darkening was noted, and THF extraction yielded only 60 mg of material. The relative amount of dibenzoselenophene was now only 5% of the biphenylene present (integration by nmr), and tlc showed the presence of four slower moving spots. Even when the reaction was allowed to proceed for only 40 hr, extensive tarring occurred.

9,9-Diphenyldibenzostannole (III).—Diphenylstannene pentamer (0.001 mol, 0.273 g) and biphenylene (0.001 mol, 0.153 g) were refluxed for 42 hr. The material soluble in THF was extracted and dried (0.250 g). Tlc and nmr showed the presence of unreacted biphenylene (0.105 g by comparison with an added reference). The extracted product was spotted on Eastman chromagram SiO_2 tlc sheets and devleoped with each of the 13 solvents (see Table I).

Vpc spectra likewise indicated the presence of III. On SE-30 (3 ft × 1/8 in., 250°), the THF extract showed a small peak (*ca.* 0.5% of total) with the retention time (20 min) of the diphenyldibenzostannole, along with seven others, and on QF-1 (12 ft × 0.25 in., 250°), the stannole peak (17 min) and six others were observed. There was only one other peak (which was of roughly equal size) within 5 min of the stannole peak on either column. Diphenyldibenzostannole was not eluted from a carbowax column (12 ft × 0.25 in., 250°) after 45 min.

The mass spectrum of the product showed relatively strong peaks at the positions and with the isotopic distribution expected for (III minus H)$^+$ and (III minus phenyl)$^+$; other peaks indicated the presence of $Ph_6Sn_2^+$ and higher molecular weight diphenyltin polymers.

Attempted Insertion of Triphenylphosphine.—Biphenylene (0.001 mol, 0.152 g) and triphenylphsphine (0.002 mol, 0.542 g) were refluxed for 30 hr. At the end of that time, biphenylene (0.13 g) was removed by sublimation, and the remaining product showed only Ph_3P and a trace of Ph_3PO (identified by mixture melting point and mass spectrometry).

Attempted Insertion of Tellurium.—Biphenylene (0.001 mol, 0.152 g) and tellurium (0.0023 mol, 0.284 g) were refluxed for 28 hr. The reaction mass was extracted with THF, yielding 0.276 g of Te (insoluble) and 0.140 g of soluble product (biphenylene, mp 108–110°). No new compounds could be detected in the recovered biphenylene by tlc or nmr.

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(4) L. Friedman and P. W. Rabideau, *J. Org. Chem.*, **33**, 451 (1968).
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(9) Kindly supplied by F. Johnson of this laboratory.
(10) F. Johnson, assigned to Dow Chemical Co., U. S. Patent 3,234,239 (Feb 8, 1966).
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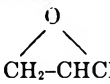
(14) J. M. Gaidis, Ph.D. Thesis, University of Wisconsin, June 1967, pp 128–129, 230.

TABLE I

Solvent	——R_f, product——	R_g, III	Resolution
	0.16, 0.34	0.16	Good
	0.13, 0.40	0.13	Good
Ligroin (bp 60–80°)	0.07, 0.15, 0.21, 0.26, 0.41	0.15	Good
CCl_4	0.21, 0.25, 0.31, 0.44, 0.59	0.44	Good
CCl_2F–$CClF_2$ (Freon 113)	0.20, 0.51	0.20	Good
	0.62–0.79	0.68	Partial
	0.53–0.70	0.58	Partial
	0.45–0.69	0.56	Partial
$CHCl_3$	0.70	0.70	Poor
$(CH_2Cl)_2$	0.58–0.68	0.65	Poor
CH_3CCl_3	0.64	0.64	Poor
C_6H_6	0.57–0 68	0 59	Poor
	0 62–0.78	0.65	Poor

Attempted Insertion of SO_2.—Biphenylene (0.001 mol, 0.151 g) was refluxed under a slow stream of SO_2 for 41 hr. There was a slight gain in weight (0.001 g *vs.* the theoretical 0.064 g), and the reaction product upon thin layer chromatography showed two new products in very low yield, but neither was the desired sulfone, and the products were not characterized.

Registry No.—Biphenylene, 259-79-0; II, 244-95-1; III, 5381-63-5.

Diaziridinones. V.[1a] Reduction by Phosphite to Carbodiimide and Peracid Oxidation of Carbodiimide to Diaziridinone[1b]

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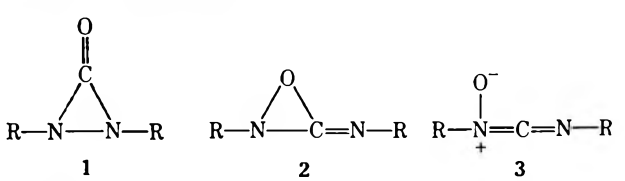
Previous papers have described the synthesis and some reactions of diaziridinones (**1**).[1a,2] Consideration of possible valence isomers **2** and **3** of **1** led to a synthesis of **1** by reaction of RNO with RNC.[1a] We consider here the possibility of preparation of **1** *via* **2** or **3** by the oxidation of a carbodiimide and the reverse problem of removal of oxygen from a diaziridinone, with conversion to a carbodiimide.



1 **2** **3**

1a, R = *t*-butyl

Peracid Oxidation of Carbodiimide.—Reaction of dicyclohexylcarbodiimide with carboxylic acids and hydrogen peroxide (eq 1) or with a carboxylic acid and a percarboxylic acid (eq 2) affords diacyl peroxides in good yield.[3] Reaction of dicyclohexylcarbodiimide with a peracid afforded the urea and diacyl peroxide in moderate yield along with a residue which could not be characterized (eq 3).[3]

$$2RNCNR + 2R'CO_2H + H_2O_2 \longrightarrow R'CO_2{-}O_2CR' + 2RNHCONHR \quad (1)$$

$$2RNCNR + R'CO_2H + R''CO_3H \longrightarrow R'CO_2{-}O_2CR'' + 2RNHCONHR \quad (2)$$

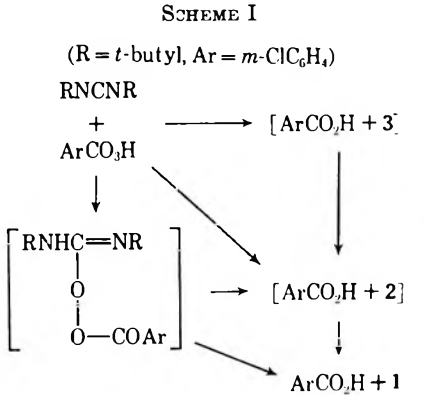
$$RNCNR + R'CO_3H \longrightarrow R'CO_2{-}O_2CR' + RNHCONHR + \text{"residue"} \quad (3)$$

Use of a more hindered carbodiimide, di-*t*-butylcarbodiimide, and *m*-chloroperbenzoic acid in methylene chloride has resulted in the isolation of di-*t*-butyldiaziridinone (**1a**) in 20% yield. The yield of **1a** was approximately the same when the reaction was carried out in a vigorously stirred two-phase system of methylene chloride and a phosphate buffer. When the reaction was carried out in carbon tetrachloride and monitored continuously by ir, diaziridinone bands (1880 cm^{-1}) built up immediately.

$$t\text{-Bu—NCN—}t\text{-Bu} + m\text{-Cl—}C_6H_4CO_3H \xrightarrow[0°]{CH_2Cl_2} \mathbf{1a}\ (20\%) \quad (4)$$

The major possibilities for diaziridinone formation are summarized in Scheme I. The generation of carboxylic acid in the reactions of Scheme I and the greater reactivity of RCO_2H in comparison with RCO_3H toward carbodiimide[3] provide additional paths for reaction accounting for the complexities in eq 3 (R = cyclohexyl) and for the low yield of **1a** in eq 4.

SCHEME I



Phosphite Reduction of Diaziridinone.—The possibility of formation of **1** *via* **2** or **3**, indicated above and in the reaction of RNO with RNC,[1a] raises the question of the reversible formation of **2** or **3** from **1**. Phenyl isocyanate, a species which appears to trap an inter-

(1) (a) Part IV: F. D. Greene and J. F. Pazos, *J. Org. Chem.*, **34**, 2269 (1969). (b) Financial support from the National Science Foundation (Grant No. GP-5527) is gratefully acknowledged.

(2) (a) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969); (b) F. D. Greene, W. R. Bergmark, and J. G. Pacifici, *ibid.*, **34**, 2263 (1969).

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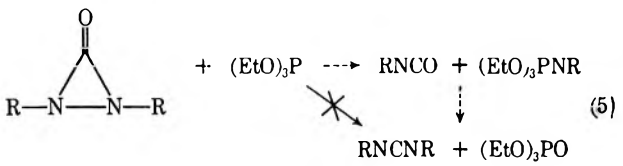
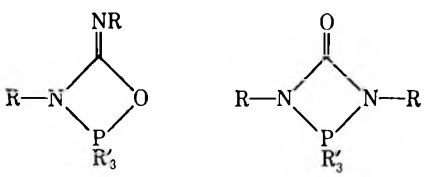
mediate (considered to be **3**) in the RNO + RNC reaction,[1a] does not react with **1** under moderate conditions, suggestive that **1** is not in facile reversible equilibrium with **3**. In view of the affinity of phosphorus compounds for oxygen,[4] reaction with **1** was examined.

Trivalent phosphorus compounds effect the deoxygenation of di-*t*-butyldiaziridinone (**1a**). Triphenylphosphine reacts with **1a** to give di-*t*-butylcarbodiimide (44%) and triphenylphosphine oxide. Reaction of **1a** with triethyl phosphite affords di-*t*-butylcarbodiimide (90%) and *t*-butyl isocyanate (4%). Analysis after partial reaction showed considerably more isocyanate (20%). The buildup of isocyanate excludes the formation of phosphate and carbodiimide by direct oxygen transfer from **1** or **2** or **3** to the phosphite.



(5)

The results suggest the formation of isocyanate and phosphinimide by reaction of **1** (or a valence isomer of **1**) with phosphite, ultimately followed by the recombination of isocyanate and phosphinimide and formation of phosphate and carbodiimide (*e.g.*, *via* **4**).[5] The prep-



4 **5**

aration of a compound assigned structure **5** (R = CH_3, R′ = Cl) by reaction of PCl_5 with RNHCONHR and its thermal decomposition to RNCO and $RNPCl_3$ with further conversion, in part, to RNCNR and $POCl_3$ has been described.[6]

Experimental Section

Reaction of *m*-Chloroperbenzoic Acid with Di-*t*-butylcarbodiimide.—The *m*-chloroperbenzoic acid was prepared by washing the commercial product with a phosphate buffer[7] until it was 99% pure by titration. To a solution of di-*t*-butylcarbodiimide[5b,8] (2.02 g, 0.013 mol) in 40 ml of CH_2Cl_2 at −15° was added a solution of *m*-chloroperbenzoic acid (2.26 g, 0.013 mol) in 30 ml of CH_2Cl_2. The reaction mixture was stirred overnight and allowed to come to 25°. The filtrate was evaporated and the residue was trap-to-trap distilled. Glpc[2] and ir analysis indicated a mixture of unchanged carbodiimide (2.2 mmol) and di-*t*-butyldiaziridinone **1a** (20% based on carbodiimide consumed).

Reaction of Di-*t*-butylcarbodiimide with *m*-Chloroperbenzoic Acid in the Presence of a Buffered Solution.—A solution of 1.242 g (7.2 mmol) of *m*-chloroperbenzoic acid (98.4%) in 30 ml of CH_2Cl_2 was vigorously stirred with 25 ml of a phosphate buffer (1.28 *M* in K_2HPO_4, 0.7 *M* in KH_2PO_4) by means of a vibrator. In this way, the mixture was thoroughly emulsified. The mixture was cooled to 0° and di-*t*-butylcarbodiimide (1.06 g, 6.85 mmol) in 10 ml of CH_2Cl_2 was added over a period of 15 min. The reaction mixture was then stirred without the ice bath for another 25 min. The CH_2Cl_2 layer was separated, dried (K_2CO_3), and evaporated. The residue was trap-to-trap distilled affording 0.539 g. Analysis by glpc showed 2.27 mmol of carbodiimide and 1.09 mmol of diaziridinone **1a** (24% yield calculated from carbodiimide consumed).

Reaction of 1a with Triphenylphosphine.—A solution of triphenylphosphine (4.62 g, 17.6 mmol) and **1a** (3.0 g, 17.6 mmol) in 20 ml of benzene was heated at reflux for 37 hr. Filtration afforded 0.82 g of triphenylphosphine oxide, mp 156–158° (lit.[9] mp 153.3°), identical with an authentic sample.[9] Analysis of the filtrate by ir and glpc indicated di-*t*-butylcarbodiimide (6.0 mmol, 45%) and unchanged **1a** (3.7 mmol, 20%). Column chromatography of the filtrate afforded additional triphenylphosphine oxide [2.2 g, total (see above) 3.02 g, 10.6 mmol, 75%] and 0.66 g of unchanged triphenylphosphine (0.66 g, 2.5 mmol, 14%). A third component, eluted in low yield, could not be obtained in pure form.

Reaction of Di-*t*-butyldiaziridinone (1a) with Triethyl Phosphite.—A solution of 1.78 g (10.7 mmol) of triethyl phosphite and 1.05 g (6.20 mmol) of **1a**[2] was sealed in a glass tube and heated at 100° for 50 hr. The resulting solution was homogeneous, clear, and colorless. Analysis by ir showed no diaziridinone but *t*-butyl isocyanate (2250 cm^{-1}) and carbodiimide (2095, 2115 cm^{-1}). Glpc analysis showed four components: *t*-butyl isocyanate, triethyl phosphite, di-*t*-butylcarbodiimide, and triethyl phosphate[10] with yields of 0.27 mmol (4.4%), 5.11 mmol, 5.64 mmol (91%), and 6.4 mmol (100%), respectively. The yields were determined by internal standardization using two independent standard solutions as checks. When 4.38 g (26.4 mmol) of of triethyl phosphite and 3.00 g (17.6 mmol) of **1a** were sealed in a tube and heated at 100° for 16 hr, 76% of the diaziridinone was consumed (by ir). The yields of the other products (glpc) were *t*-butyl isocyanate, 3.00 mmol (22.4%); di-*t*-butylcarbodiimide, 7.55 mmol (56.5%); triethyl phosphate, 8.15 mmol (60.8%); triethyl phosphite, 7.70 mmol (yields are based on the diaziridinine consumed).

In another experiment a solution of 2.92 g (17.6 mmol) of triethyl phosphite and 3.00 g (17.6 mmol) of **1a** was heated at 60–100°. At an early stage of the reaction the carbodiimide and isocyanate bands were of about equal intensity; in the later stages the intensity ratio heavily favored the carbodiimide.

Attempted Reaction of Sodium Diethyl *t*-Butylamidophosphate with Di-*t*-butyldiaziridinone (1a).—To a solution of 8.80 mequiv of sodium diethyl *t*-butylamidophosphate in 28 ml of 1,2-dimethoxyethane (distilled from sodium and benzophenone ketyl), prepared[5b] from diethyl *t*-butylamidophosphate (Aldrich Chemical Co.) and sodium hydride as base, under dry nitrogen, was added 1.72 ml (1.50 g, 8.80 mmol) of **1a** in 10 ml of dimethoxyethane. No change (ir) was observed after 1 hr at room temperature and 6.5 hr at 75°. To ascertain the activity of the amidophosphate anion after this treatment, 0.20 ml (174 mg, 1.75 mmol) of *t*-butyl isocyanate was added and the solution was heated at 75° for 15 min.[5b] Complete conversion to di-*t*-butylcarbodiimide was clearly indicated by the complete disappearance of the 2250-cm^{-1} isocyanate band and the appearance of the characteristic 2100-cm^{-1} doublet of di-*t*-butylcarbodiimide of appropriate intensity. This resulting mixture was heated an additional 40 hr at reflux with no change detected.

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

Registry No.—**1a**, 19656-74-7; *m*-chloroperbenzoic acid, 937-14-4; di-*t*-butylcarbodiimide, 691-24-7; triethyl phosphite, 122-52-1.

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(6) H. Ulrich and A. A. R. Sayigh, *ibid.*, **30**, 2779 (1965).

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(10) Prepared by the method of A. J. Burn and J. I. G. Cadogan, *Chem. Ind.* (London), 736 (1963), bp 114–119° (25 mm) [D. P. Evans, W. C. Davies, and W. J. Jones, *J. Chem. Soc.*, 1310 (1930), give bp 215° (760 mm)].

Synthesis of 2,3′-Bipyrrole. Denitrosation in the Knorr Pyrrole Synthesis[1]

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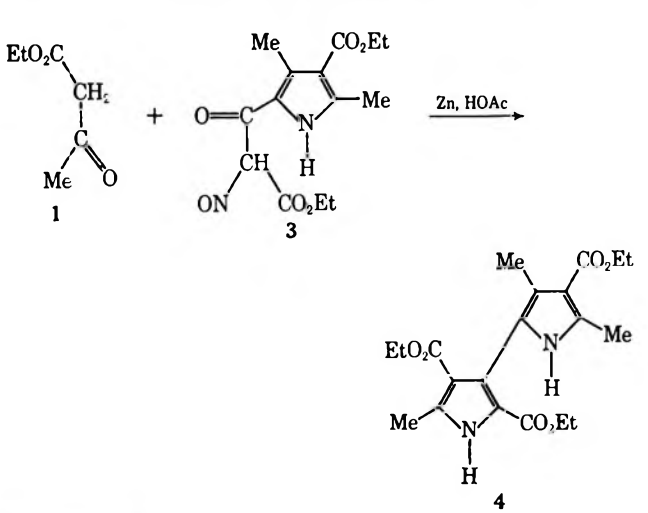
The 2,2′-bipyrrolylpyrrolylmethene metabolite, prodigiosin, has been widely investigated as a possible antimicrobial agent and has shown some antifungal[3] and antimalarial[4] activity. In a consideration of the influence of structure on activity, it was of interest to initiate a study directed at the synthesis and antimicrobial evaluation of congeneric 2,3′-bipyrrolylpyrrolylmethenes. In this communication we describe the synthesis of a 2,3′-bipyrrole and unexpected results in the frequently employed Knorr pyrrole synthesis.

In contrast with the numerous syntheses of 2,2′-bipyrroles,[5] only one synthesis of a 2,3′-bipyrrole has been reported.[6] In this earlier work the condensation of ethyl 2-amino-3-oxo-3-(3,4-dimethylpyrrol-2-yl)-propanoate hydrochloride with ethyl acetoacetate (**1**) in the presence of sodium acetate and potassium acetate is described as yielding 2-(2-carboxy-4-ethoxycarbonyl-5-methylpyrrol-3-yl)-3,5-dimethylpyrrole. The condensation in this case is seen to be accompanied by hydrolysis of one of the ester groupings. An attempt by us to extend this procedure to the reaction of ethyl 2-amino-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate hydrochloride (**2**) and ethyl acetoacetate was unsuccessful. Nevertheless, from the reaction of ethyl 2-nitroso-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (**3**), ethyl acetoacetate, and zinc in acetic acid, we were able to obtain 2-(2,4-diethoxycarbonyl-5-methylpyrrol-3-yl)-3,5-dimethyl-4-ethoxycarbonylpyrrole (**4**) in a low yield (6%). Interestingly, a number of years ago, Knorr and Lange[7] reported obtaining better pyrrole yields in several examples starting with aminoacetophenone hydrochloride instead of *via* the *in situ* reduction of nitrosoacetophenone, as in the usual procedure.



Because of the poor yield obtained in the otherwise successful Knorr synthesis of **4** we were led to investigate the possibility of improvement of these results through a better understanding of the influence of reaction conditions on yield. We have found, when the synthesis is attempted in a helium atmosphere instead of the usual ambient laboratory conditions, that none of **4** is formed and instead the denitrosation[8] product, ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (**5**), is obtained in a high yield (92%). These surprising results prompted a similar comparison of the Knorr pyrrole synthesis with ethyl nitrosobenzoylacetate (**6**) and ethyl acetoacetate. Again, under ordinary laboratory conditions the expected 2,4-diethoxycarbonyl-5-methyl-3-phenylpyrrole (**7**) resulted, but, when the reaction was carried out in a helium atmosphere, ethyl cinnamate (**8**), the product from denitrosation, reduction, and dehydration of ethyl nitrosobenzoylacetate, was the major product, and none of **7** was detected. Finally, the zinc dust in acetic acid reduction of a mixture of ethyl nitrosoacetoacetate (**9**) and ethyl acetoacetate is a standard procedure for the synthesis of 2,4-diethoxycarbonyl-3,5-dimethylpyrrole (Knorr's pyrrole **10**).[9] However, when ethyl nitrosoacetoacetate alone is treated with zinc dust in acetic acid under conditions comparable to those used in the standard synthetic procedure for **10**, but employing an atmosphere of argon, Knorr's pyrrole (13%) is formed directly reflecting denitrosation of some of the starting nitroso derivative. Moreover, a small amount of the denitrosated product, ethyl acetoacetate (3.9%), was also isolated from the reaction. The importance of the atmosphere (presumably oxygen) on the success of the Knorr pyrrole synthesis in the examples reported herein is clear and it appears likely that this may be a general phenomenon. The experimental evaluation of its scope and the role of the atmosphere is planned for investigation.

The nitrosation of ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (**11**) led to two products in a ratio of *ca.* 1:1. These are evidently the oximino and nitroso derivatives,[10] with the latter showing an ir absorption band at 8.28 μ corresponding to a dimer.[10d] We were able to isolate the oximino derivative in an analytically pure form. Upon standing in ethyl acetate, it isomerized to yield a mixture like that initially obtained from the nitrosation reaction.

(1) We are grateful for a generous grant from the Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Inc., which was of aid in this investigation. We are also pleased to acknowledge the help of T. Hardy, D. M. Mourad, and L. F. Wendt with certain phases of the experimental work.

(2) National Science Foundation Undergraduate Research Participant.

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Experimental Section[11]

Ketones.—Ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)-propanoate (11)[12] and ethyl benzoylacetate[13] were synthesized as described in the literature. The ethyl acetoacetate was a redistilled commercial product.

Nitroso Ketones.—The general procedure of Barltrop and coworkers[14] using isoamyl nitrite and hydrogen chloride with the ketone was followed. A minor variation in the present work was the use of tetrahydrofuran as the solvent instead of ethyl ether. Ethyl nitrosoacetoacetate (9) (29–43%) showed bp 122–125° (2.6–3.0 mm), n^{24}D 1.4562 (lit.[15] n^{25}D 1.4557); ethyl nitrosobenzoylacetate (6), mp 119–120° (lit.[16] 120–121°).

The nitrosation of ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (11) led to a product (3) in high yield (95% calcd for the nitroso derivative) which was found by tlc (SilicAR TLC-7G, 5% methanol–95% chloroform) to be a *ca.* 1:1 mixture of two components. When the slower moving component was allowed to stand in ethyl acetate for 18 hr, it was found that two components having the same R_f values as those in the original mixture were again present. The isolation of the component with the higher R_f by fraction crystallization was unsuccessful, but the component with the lower R_f was obtained from ether in this way. The crystalline white solid melted at 146–148° dec.

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 54.18; H, 5.84; N, 9.02. Found: C, 54.03; H, 5.72; N, 8.96.

The ir (KBr) for the higher R_f fraction showed absorption bands at 2.99 (pyrrole NH), 5.74 (side chain ester C=O), 5.95 (ring ester C=O), 6.18 (keto C=O), 8.28 μ (nitroso dimer);[10d] the lower R_f fraction, 2.87 (oximino OH), 3.07 (pyrrole NH), 5.74 (side chain ester C=O), 5.91 (ring ester C=O), 6.21 (keto C=O), 6.68 μ (oximino C=N).[17]

Ethyl 2-Amino-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate Hydrochloride (2).—A solution of 3.1 g of the mixture 3 obtained from the nitrosation of ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate in 50 ml of 95% ethyl alcohol and 1.67 ml of 6 *N* hydrochloric acid was shaken with 0.3 g of 5% palladium-on-charcoal catalyst in an atmsophere of hydrogen (initial pressure 42 psig) in a Burgess-Parr hydrogenator. Hydrogenation stopped with the uptake of 41% of the amount of hydrogen calculated for the nitroso derivative. Removal of the catalyst followed by crystallization of the solid product from a mixture of absolute ethanol and ethyl ether, containing hydrogen chloride, gave the amine hydrochloride 2. When heated this compound starts to decompose at *ca.* 188°.

Anal. Calcd for $C_{14}H_{21}ClN_2O_5$: C, 50.52; H, 6.26; N, 8.41. Found: C, 50.37; H, 6.19; N, 8.59.

2-(2,4-Diethoxycarbonyl-5-methylpyrrol-3-yl)-3,5-dimethyl-4-ethoxycarbonylpyrrole (4).—Following the literature description for the synthesis of Knorr's pyrrole,[9] a solution of 5.0 g of ethyl 2-nitroso-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)-propanoate (11) and 2.1 g of ethyl acetoacetate in 100 ml of glacial acetic acid was treated with 5.0 g of zinc dust. The mixture was stirred and heated to 70° for 50 min, and the crude product was isolated as described in the literature reference. Column chromatography of the crude reaction product (SilicAR CC-7, ethyl acetate–hexane, 1:1), decolorization of the chromatograph fraction with Norit in 95% ethyl alcohol, and crystallization from the same solvent gave 0.40 g (6%) of the bipyrrole (4), mp 168.0–168.5°. The nmr spectrum for this compound shows the following: ethyl CH_3, δ 1.25 (pentuplet, relative intensity 9); ring CH_3, 2.04, 2.49, 2.53 (singlets, 3 each); ethyl CH_2, 4.23 (multiplet, 6); pyrrole NH, 8.65, 9.91 (broad singlets, 1 each).

Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.52; H, 6.71; N, 7.17. Found: C, 61.31; H, 6.69; N, 7.30.

2,4-Diethoxycarbonyl-5-methyl-3-phenylpyrrole (7).—Essentially the procedure used for the synthesis of the bipyrrole was followed using 2.2 g of ethyl nitrosobenzoylacetate, 1.3 g of ethyl acetoacetate, 30 ml of glacial acetic acid, and 2.0 g of zinc dust. The reaction mixture was held at 100–110° for 45 min in this synthesis. The product, mp 124–126°, isolated directly from the reaction mixture, weighed 2.0 g (67%). A sample recrystallized from cyclohexane–benzene and three times from 95% ethyl alcohol melted at 127.0–128.0° (lit.[18] 117–119°).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.87; H, 6.43; N, 4.59.

Denitrosation of Nitroso Ketones. (a) **Ethyl Nitrosoacetoacetate (9).**—Fifty grams of zinc dust was added portionwise to a stirred solution of 12.3 g of the nitroso derivative in 200 ml of glacial acetic acid. During this period the temperature was held to a maximum of 70° and, after all of the zinc had been added, the mixture was stirred and refluxed for 1 hr. The reaction system was maintained in an atmosphere of argon during the entire operation. The white solid that separated, 2.4 g (13%), when the reaction mixture was poured into water, was shown to be 2,4-dimethyl-3,5-diethoxycarbonylpyrrole (10) by its mp 132–134° (lit.[9] 136–137°) and a comparison of its infrared spectrum with that of an authentic sample. The aqueous phase from which 10 had separated was neutralized with sodium bicarbonate and extracted with ether. After drying the extract with magnesium sulfate and evaporating the solvent, an oil remained. This was shown by vpc analysis (Carbowax 20M) to contain ethyl acetoacetate (1) (3.9%).

(b) **Ethyl Nitrosobenzoylacetate (6).**—A mixture of 1.1 g of the nitroso compound and 0.65 g of ethyl acetoacetate in 45 ml of glacial acetic acid was treated with 15.3 of zinc dust as in the preceding experiment. However, in this case the reaction mixture was held at 70° for 10 min after addition of all of the zinc and was not heated further. Also, the reaction was conducted in an atmosphere of helium. The work-up was the same as in the above example and 0.76 g of an oil was obtained. Vpc analysis (diethylene glycol succinate) showed the presence of four components. Ethyl cinnamate (8), the major component, and ethyl acetoacetate were identified by "spiking." The cinnamate ester was also isolated and identified by comparison of its ir spectrum with that of an authentic sample.

(c) **Ethyl 2-Nitroso-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (3).**—The reaction was carried out as in the above example using 5.0 g of 3, 2.1 g of ethyl acetoacetate, 100ml of glacial acetic acid, and 13.5 g of zinc dust. A reaction temperaturd of 100–110° was used. The bulk of the solvent was evaporated at reduced pressure, the remaining acetic acid was neutralized with aqueous sodium bicarbonate, and the crude product was extracted with ethyl ether. Column chromatography (SilicAR CC-7, ethyl acetate–hexane) yielded 4.17 g (92%) of ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (11), mp 143° (lit.[12] 140.5–142°), having an ir spectrum identical with that of an authentic sample.

Registry No.—2, 24744-71-6; 3, 24744-72-7; 4, 24744-73-8; 7, 3651-13-6; 9, 24744-75-0.

(11) Melting points were determined with a Fisher-Johns apparatus and are uncorrected; ir spectra, Beckman IR-5; nmr spectrum, Varian HA-100, in $CDCl_3$ using the TMS lock signal; vpc, Model A-100-C and A-700 Aerographs, Wilkens Instrument Co., using columns from the same company. Elemental analyses are by the Berkeley Analytical Laboratory.

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Selective Photocoupling of Perfluorodiacyl Fluorides

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Photolysis of monofunctional perfluoroacyl fluorides has been described as a route to nonfunctional fluorocarbons[1] and fluorocarbon ethers.[2] However, irradia-

(1) J. F. Harris, Jr., *J. Org. Chem.*, **30**, 2182 (1965).

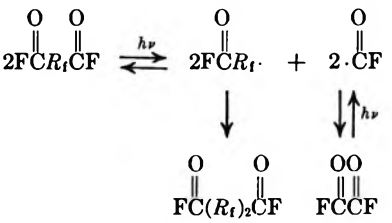
(2) British Patent 1,038,365; German Patent 1,249,247.

TABLE I
PHOTOLYSIS OF PERFLUORODIACYL FLUORIDES

Diacyl fluoride	Product	Conversion (yield, %)
$OFC(CF_2)_3CFO$	$OFC(CF_2)_6CFO$[a]	78 (62)
$OFC(CF_2)_6CFO$	$OFC(CF_2)_{12}CFO$	76 (41)
$OFCCF_2CF_2OCF_2CF_2CFO$	$OFC(CF_2CF_2OCF_2CF_2)_2CFO$	72 (62)
$OFC(CF_2CF_2OCF_2CF_2)_2CFO$	$OFC(CF_2CF_2OCF_2CF_2)_4CFO$[b]	53 (41)
$OFCCF_2OCF_2CFO$	$OFC(CF_2OCF_2)_2CFO$	52 (35)

[a] An 11% yield of $OFC(CF_2)_9CFO$ was also isolated. [b] Photolysis carried out at reduced pressure (100 mm).

tion of perfluoroglutaryl fluoride produced an inseparable, solid reaction product presumed to be a mixture of long-chain polyacyl fluorides.[1] It is the object of this paper to describe a technique wherein fluorocarbon diacyl fluorides are photolyzed under controlled conditions to produce good yields of higher molecular weight diacyl fluorides. As will be shown, further telomerization and other side reactions are substantially avoided by controlling the residence time of the desired products in the photolysis zone. Since oxalyl fluoride is known to generate the fluoroformyl radical on photolysis, it is also important to remove the volatile by-products so that fluoroformyl radical recombination is minimized and maximum photolytic efficiency maintained.



These requirements can be achieved conveniently in a continuous process by utilizing the apparatus shown in Figure 1 which relies upon differences in volatility between the starting materials and the products. The technique affords good yields of the desired products and is readily adaptable to the conversion of pound quantities of starting diacyl fluorides.

The process consists of refluxing a fluorocarbon diacyl fluoride, with or without a suitable codistilling solvent, into the photoreactor zone where the liquid phase is photolyzed and then returned to the flask. During the course of the reaction, the higher diacyl fluoride produced, hereinafter referred to as "dimer," is returned to the flask and remains therein while the starting material continues to reflux and is recycled to the photolysis chamber. In general, the residence time is determined empirically and the return tube leading from the photolysis chamber to the Vigreux column is made with appropriate dimensions to accomplish the desired residence time. It is necessary to increase gradually the temperature of the flask in order to ensure vaporization of the progressively decreasing amount of starting material. Thus, the extent of reaction can be followed by monitoring the pot temperature or more exactly by vapor phase chromatographic analysis of aliquots withdrawn from the flask. The uncondensed by-products of the reaction, primarily oxalyl fluoride and minor amounts of carbonyl fluoride and carbon dioxide, are removed effectively from the system by volatilization.

The conversions to linear, dimer products (50–80%) indicate that the predominant reaction is radical–radical combination. Other than those derived from the

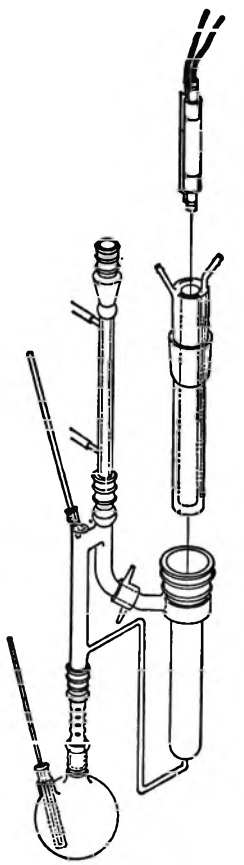


Figure 1.—Photodimerization reactor.

fluoroformyl radical, the by-products of the reaction are generally higher boiling materials which are probably branched and result from the addition of perfluoroalkyl radicals to the oxygen of an acyl fluoride group.[1,3]

In all but one example, the reactions shown in Table I were carried out at atmospheric pressure since the volatilities of the starting fluorocarbon diacyl fluorides were sufficient to permit convenient vaporization. Since the photoreactor zone had a holdup volume of about 40 cc, codistilling inert fluorocarbon solvents were used in reactions employing limited amounts of starting materials. The use of fluorocarbon solvents in the photodimerization of perfluorodiacyl fluorides resulted in up to 97% conversions of starting material into dimerized products. The good conversions to the desired products and minimal amounts of higher homologs attest to the effectiveness of using volatility differences to control residence time in the photolysis zone.

It was difficult to achieve a satisfactory yield of $OFC(CF_2OCF_2)_2CFO$ from the photolysis of $OFCCF_2$-

(3) The nature of the high boiling products has been studied in detail and will be reported in a forthcoming paper by Dr. J. R. Throckmorton.

OCF_2CFO because of condenser losses. The condenser was required to return starting material (bp 38°) to the system yet not condense oxalyl fluoride by-product (bp 6°). Satisfactory yields were obtained only with careful temperature control while employing four 15-watt, low-pressure ultraviolet lamps rather than a 450-watt medium-pressure unit. A low yield of $OFC(CF_2OCF_2)_3CFO$ was also obtained.

It was found convenient to carry out the photolysis of $OFC(CF_2CF_2OCF_2CF_2)_2CFO$ under reduced pressure to effect adequate boil-up rates of the starting material. The use of vacuum also facilitated the removal of the low boiling uncondensed by-products, *e.g.*, oxalyl fluoride, and as a consequence, substantially reduced the required photolysis time necessary to achieve good conversions. Conventional pressure-reducing means were connected to the top of the condenser and, to ensure a smooth operation under reduced pressure, a ballast or vacuum surge chamber was incorporated into the system. A vacuum of 100 mm was achieved easily and although the boil-up rate was somewhat less than in other reactions; the preparation of $OFC(CF_2CF_2OCF_2CF_2)_4CFO$ proceeded smoothly.

Two derivatives of the above diacyl fluoride were also prepared in the course of this investigation. Reaction with ammonia in ether afforded the diamide. Dehydration of the diamide to the corresponding perfluoroether dinitrile was accomplished by coating an

$$OFC(CF_2CF_2OCF_2CF_2)_4CFO \xrightarrow{NH_3} H_2NC(=O)(CF_2CF_2OCF_2CF_2)_4C(=O)NH_2 \xrightarrow{P_2O_5} N{\equiv}C(CF_2CF_2OCF_2CF_2)_4C{\equiv}N$$

etheral solution of the diamide on P_2O_5, evaporating the ether and heating the resulting P_2O_5–amide mixture to 220°. The yield of dimitrile for the two steps was 63%.

Experimental Section

Infrared spectra were measured on a Perkin-Elmer Model 21 double beam instrument using NaCl plates. The vpc unit used for monitoring the reactions was an F & M Model 500 gas chromatograph employing a 12 ft × 3/8 in. column packed with 33% FS-1265 (fluorosilicone) on Chrome P. Nuclear magnetic resonance measurements were made with a Varian V-4300-2 instrument operating at 40.0 Mc and utilizing an internal standard of $CFCl_3$ for the determination of chemical shifts. The values reported in Table II are ϕ^* values[4] at a dilution of 10–25%. Trifluoroacetic acid is ϕ^* 76.5 on this scale.

Diacyl fluoride starting materials were prepared from the corresponding diacyl chlorides by treatment with potassium fluoride.

General Photolysis Procedure.—All of the reactions were carried out in essentially the same manner, using the apparatus shown in Figure 1 or larger variations thereof.

The perfluorodiacyl fluoride starting material was heated with magnetic stirring in the flask until it refluxed vigorously through the Vigreux column. The vapors were condensed in the upright condenser and dripped into the photoreactor zone. The photoreactor consisted of a water-cooled 7 60–50 jointed quartz immersion cell (20 × 80 × 2 mm), a photolysis chamber with a hold-up volume of about 40 cc, a wound 36 in. length of 1/8 in. polytetrafluoroethylene cord placed as a distributor in the top of the cell, and a Hanovia 450-watt ultraviolet immersion lamp. Aluminum foil was wrapped around the reactor to act as a reflector. The photolyzed reaction mixture was carried from the bottom of the photoreactor into the Vigreux column from which the unreacted starting material was vaporized and recycled while the higher boiling products remained in the flask. The process was continuously carried out in this manner at atmospheric pressure, the heating bath being maintained about 50° higher than the pot temperature to facilitate boiling. After the reaction was complete, the liquids in the flask and photoreactor were combined and separated by distillation.

Photolysis of $OFC(CF_2)_3CFO$.—A sample of perfluoroglutaryl fluoride (236 g, 0.97 mol) was placed in a 250-cc flask containing a magnetic stirring bar and the flask attached to the photoreactor as shown in Figure 1. At reflux, the initial pot and head temperatures were 48 and 43°, respectively. After 68 hr of photolysis, the pot temperature had risen to 109° and the head temperature to 46°. Distillation of the product mixture afforded 118 g (78% conversion, 62% yield) of perfluorooctanedioyl fluoride, bp 70° (155 mm), identified by spectral comparisons with an authentic sample. Perfluoroundecanedioyl fluoride, amounting to 19.2 g (14% conversion, 11% yield), was obtained as a higher boiling fraction, bp 89° (30 mm).

Photolysis of $OFC(CF_2)_6CFO$.—In this experiment, 110.4 g (0.28 mol) of perfluorooctanedioyl fluoride was photolyzed in a similar manner. The flask (60 cc) was heated overnight to maintain 110° material flowing through the photolysis chamber. When the pot temperature reached 170°, the reaction was terminated and the contents of the flask and photolysis chamber were combined. Distillation of the combined liquid yielded 50 g of starting material in the forecut [bp 70° (155 mm)], 15 g of an intermediate cut, and 40 g (76% conversion, 41% yield) of the desired perfluorotetradecanedioyl fluoride, $OFC(CF_2)_{12}CFO$, bp 110–113° (20 mm). The structure was confirmed by ^{19}F nuclear magnetic resonance and infrared spectroscopy.

Hydrolysis of the diacyl fluoride yielded perfluorotetradecanedioic acid, $HO_2C(CF_2)_{12}CO_2H$, a colorless solid, mp 185–188° (lit.[5] mp 191–193°).

Anal. Calcd for $C_{14}F_{24}H_2O_4$: C, 24.35; F, 66.1; H, 0.3; mol wt, 690; neutral equiv, 345. Found: C, 24.5; F, 64.9; H, 0.5; mol wt, 649; neutral equiv, 328.

Photolysis of $OFCCF_2CF_2OCF_2CF_2CFO$.—Following the procedure outlined above, 1250 g (4.03 mol) of perfluorooxydipropionyl fluoride,[6] $OFCCF_2CF_2OCF_2CF_2CFO$, was heated in a flask, previously purged with nitrogen, to maintain a steady flow of condensate through the photolysis chamber. Reaction was continued for 100 hr at which time the pot temperature was 146.5° and the head temperature was 88°. Distillation of the combined flask and photolysis chamber contents produced 78 g of unreacted starting material and 658 g (72% conversion, 62.5% yield) of the desired product, $OFC(CF_2CF_2OCF_2CF_2)_2CFO$, bp 88° (100 mm). The structure was confirmed by ^{19}F nuclear magnetic resonance and infrared and mass spectroscopy.

After reaction of the diacyl fluoride with excess methanol in the presence of sodium fluoride, distillation afforded the corresponding dimethyl ester, $CH_3O_2C(CF_2CF_2OCF_2CF_2)_2CO_2CH_3$, bp 98° (2 mm).

Anal. Calcd for $C_{12}F_{16}H_6O_6$: C, 26.1; F, 55.3. Found: C, 26.1; F, 55.3.

Photolysis of $OFC(CF_2CF_2OCF_2CF_2)_2CFO$.—A sample of $OFC(CF_2CF_2OCF_2CF_2)_2CFO$ (167.7 g, 0.318 mol) was placed in the reactor shown in Figure 1. The apparatus was modified by connecting a 1-l. ballast or surge chamber to the top of the condenser through vacuum tubing in order to carry out the process under a reduced pressure (100 mm). The flask was heated to about 90° and the head temperature was maintained at about 79°. During 5 hr of photolysis, the pot temperature was raised to about 190° to maintain constant boil-up. The liquid contents of the flask and photolysis chamber were combined and distilled to yield 40.4 g (in three fractions) of the starting material and 61.5 g (53% conversion, 41% yield) of the desired product, $OFC(CF_2CF_2OCF_2CF_2)_4CFO$, bp 87–90° (0.9 mm). The structure was confirmed by ^{19}F nuclear magnetic resonance, infrared and mass spectroscopy and elemental analysis.

Anal. Calcd for $C_{18}F_{34}O_6$: C, 22.6; F, 67.4. Found: C, 22.7; F, 67.0.

Reaction of the diacyl fluoride (191 g, 0.199 mol) with excess ammonia in diethyl ether afforded 161 g (85%) of the diamide after filtration to remove NH_4F and evaporation of the ether filtrate.

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(6) British Patent 858,671; V. Ya Kazakov, R. A. Dzerzhinskoya, V. I. Tsimbalist, and E. A. Shishkin, *Zh. Obshch. Khim.*, **36**, 1807 (1966).

TABLE II

^{19}F NUCLEAR MAGNETIC RESONANCE SPECTRA

Formula	Registry no.	Group	ϕ*
$OF\overset{a}{C}\overset{b}{C}F_2CF_2CFO$	678-78-4	CFO	−24.1
		CF_2 (a)	118.2
		CF_2 (b)	123.7
$OF\overset{a}{C}\overset{b}{C}F_2(CF_2)_4CF_2CFO$	24647-09-4	CFO	−24.2
		CF_2 (a)	118.1
		CF_2 (b)	122.1
$OF\overset{a}{C}\overset{b}{C}F_2\overset{c}{C}F_2(CF_2)_5CF_2CF_2CFO$	24647-10-7	CFO	−24.0
		CF_2 (a)	118.4
		CF_2 (b)	122.4
		CF_2 (c)	121.7
$HO_2C\overset{a}{C}F_2\overset{b}{C}F_2\overset{c}{C}F_2(CF_2)_5CF_2CF_2CO_2H$	24647-11-8	CF_2 (a)	118.8
		CF_2 (b)	122.6
		CF_2 (c)	121.6
$OF\overset{a}{C}\overset{b}{C}F_2\overset{c}{C}F_2(CF_2)_8CF_2CF_2CFO$	24647-12-9	CFO	−24.0
		CF_2 (a)	118.6
		CF_2 (b)	122.7
		CF_2 (c)	121.9
$HO_2C\overset{a}{C}F_2\overset{b}{C}F_2\overset{c}{C}F_2(CF_2)_8CF_2CF_2CO_2H$	2822-93-7	CF_2 (a)	119.2
		CF_2 (b)	122.9
		CF_2 (c)	121.8
$OF\overset{a}{C}\overset{b}{C}F_2CF_2OCF_2CF_2CFO$	1428-40-6	CFO	−23.6
		CF_2 (a)	121.6
		CF_2 (b)	85.7
$(OF\overset{a}{C}\overset{b}{C}F_2CF_2O\overset{c}{C}F_2\overset{d}{C}F_2)_2$	24647-14-1	CFO	−23.6
		CF_2 (a)	121.5
		CF_2 (b)	86.0
		CF_2 (c)	83.3
		CF_2(d)	125.9
$(CH_3O_2C\overset{a}{C}F_2\overset{b}{C}F_2O\overset{c}{C}F_2\overset{d}{C}F_2)_2$	24689-55-2	CF_2 (a)	122.2
		CF_2 (b)	85.7
		CF_2 (c)	83.3
		CF_2 (d)	125.9
$OF\overset{a}{C}\overset{b}{C}F_2O[\overset{c}{C}F_2\overset{d}{C}F_2CF_2CF_2O]_3CF_2CF_2CFO$	24647-15-2	CFO	−23.6
		CF_2 (a)	121.2
		CF_2 (b)	85.4
		CF_2 (c)	83.0
		CF_2 (d)	125.5
$H_2NC(O)\overset{a}{C}F_2\overset{b}{C}F_2O(\overset{c}{C}F_2\overset{d}{C}F_2CF_2CF_2O)_3CF_2CF_2C(O)NH_2$	24647-16-3	CF_2 (a)	122.7
		CF_2 (b)	85.0
		CF_2 (c)	83.2
		CF_2 (d)	126.0
$N\overset{a}{C}\overset{b}{C}F_2\overset{c}{C}F_2O(\overset{d}{C}F_2CF_2CF_2CF_2O)_3CF_2CF_2CN$	23790-63-8	CF_2 (a)	109.0
		CF_2 (b)	87.3
		CF_2 (c)	83.5
		CF_2 (d)	126.0
$OFCCF_2OCF_2CFO$	21297-64-3	CFO	−13.3
		CF_2	76.7
$OF\overset{a}{C}\overset{b}{C}F_2OCF_2CF_2OCF_2CFO$	24647-19-6	CFO	−13.3
		CF_2 (a)	77.0
		CF_2 (b)	88.2
$CH_3O_2C\overset{a}{C}F_2\overset{b}{C}F_2OCF_2CF_2OCF_2CO_2CH_3$	24647-20-9	CF_2 (a)	77.9
		CF_2 (b)	88.8
$(OF\overset{a}{C}\overset{b}{C}F_2OCF_2\overset{c}{C}F_2)_2O$	24689-56-3	CFO	−13.2
		CF_2 (a)	77.2
		CF_2 (b)	88.5
		CF_2 (c)	88.8

The diamide (161 g, 0.169 mol) was dissolved in 500 cc of ether and poured onto 100 g of P_2O_5. The slurry was dried in a rotating evaporator and heated to 220° for 2 hr. Upon application of a vacuum to the flask, the colorless liquid dinitrile distilled into the collection flask. Redistillation afforded 144.5 g (75%) of $N{\equiv}C(CF_2CF_2OCF_2CF_2)_4C{\equiv}N$, bp 125° (10 mm). The infrared spectrum shows the nitrile absorption at 4.42 μ.

Photolysis of $OFC(CF_2CF_2OCF_2CF_2)_2CFO$ in Solvent.—A mixture of 944 g (1.79 mol) of $OFC(CF_2CF_2OCF_2CF_2)_2CFO$ and 408 g of perfluorotributylamine solvent was photolyzed following the general procedure outlined above, using a 1-l. flask and reduced pressure (100 mm). The initial pot and head temperatures were 97 and 91°, respectively. After 54 hr of photolysis, the temperatures had risen to 136 and 113°, respectively. Distillation of the combined flask and photolysis chamber contents produced a forecut containing unreacted starting material and solvent and a 413.2 g fraction (48.1% yield) of the desired product, $OFC(CF_2CF_2OCF_2CF_2)_4CFO$.

Photolysis of $OFCCF_2OCF_2CFO$.[7]—A mixture of 390 g (1.85 mol) of perfluorooxydiacetyl fluoride, bp 38°, and 2197 g of FC-78[8] were photolyzed in a larger unit than that described above. Ultraviolet light was supplied by four 15-watt low-pressure mercury lamps (2537 Å). The reactor temperature was maintained at about 30° during the 10 days of the run. The yield of $OFC(CF_2OCF_2)_2CFO$, bp 82°, was 101 g (52% conversion).

Reaction of the diacyl fluoride with methanol at 0° in the presence of excess sodium fluoride produced the corresponding dimethyl ester, $CH_3O_2C(CF_2OCF_2)_2CO_2CH_3$, bp 123.5° (50 mm).

Anal. Calcd for $C_8F_8H_6O_6$: C, 27.5; F, 43.5; H, 1.7; mol wt, 350. Found: C, 27.5; F, 43.6; H, 1.8; mol wt, 339 (in acetone).

Acknowledgment.—The authors wish to express their gratitude to Dr. J. J. McBrady for infrared and ^{19}F nmr spectra, to M. S. Kulver for mass spectra, and to Mr. P. B. Olson for elemental analysis.

(7) The authors are indebted to Dr. W. B. Isaacson and Dr. S. T. Ting for carrying out this experiment in a wiped-film photoreactor. The description of this new photoreactor has been published in *Ind. Eng. Chem., Fundam.*, **9**, 171 (1970).

(8) A perfluorocarbon inert liquid, bp 50–52°, sold by the 3M Company, St. Paul, Minn.

The Synthesis of 2,5-Dialkoxy-1,4-diphosphoniacyclohexane Salts[1]

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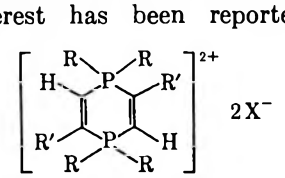
A new organophosphorus heterocycle, 1,4-diphosphoniacyclohexadiene-2,5 (**1**), of both theoretical and biological interest has been reported recently.[4-9]



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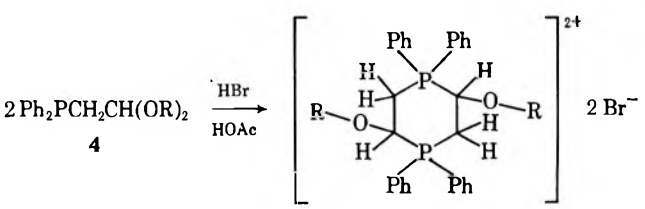
In an attempt at developing a new synthetic route to this system, we have found that a tetrahydrofuran solution of lithium diphenylphosphide (**2**) reacts with the dimethyl and diethyl acetals of chloroacetaldehyde (**3**) to give the corresponding acetal of diphenylphosphinoacetaldehyde (**4**) (eq 1).

$$\underset{\mathbf{2}}{Ph_2PLi} + \underset{\mathbf{3}}{ClCH_2CH(OR)_2} \xrightarrow{THF} \underset{\mathbf{4}}{Ph_2PCH_2CH(OR)_2} + LiCl \quad (1)$$

R = Me, Et

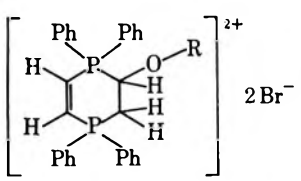
Upon reaction of **4** with hydrogen bromide in boiling glacial acetic acid, the new 2,5-dialkoxy-1,4-diphosphoniacyclohexane dibromide (**5**) could be isolated (eq 2).



5 (2)

R = Me, Et

No mono- (**6**) or di- (**1a**) unsaturated heterocycles were isolated.



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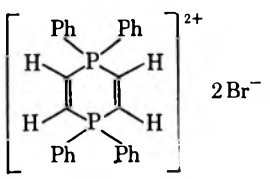
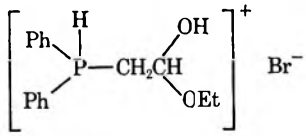


1a

It is surprising that under these conditions no **1a** is isolated since this could occur *via* the aldehyde, the acetylene, or even the dealcoholization of **5**. Dealcoholization of isolated **5** to **1a** was attempted employing boron trifluoride etherate with no success. At present the stability of **5** to Lewis acids is not clear. It may involve interaction of the unshared pair of electrons on the oxygen with the positive phosphorus.

The possibility that the compound which we have designated **5b** is actually the hemiacetal phosphine hydrobromide (**7**) has been eliminated by ir spectrophotometry. The ir spectrum of **5b** contains no band between 2000 and 2500 cm^{-1}. It has been shown that phosphine hydrobromides exhibit a fairly intense peak in this region.[6] Furthermore, there was no change in the nmr spectrum of a $CDCl_3$ solution of **5b** upon treatment with D_2O. It is known that the proton of a phosphine hydrobromide undergoes rapid exchange with D_2O under these conditions.[6]



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The structure of compound **5b** was unequivocally determined with the aid of its 100-MHz spectrum. The complex downfield nmr pattern centered at 7.90 ppm

(1) Taken in part from the dissertation of K. C. Hansen, Tulane University, 1967.

(2) NASA Fellow at Tulane University, 1964–1967.

(3) NASA Fellow, 1966–1967; NDEA Fellow, 1967–1969; NSF Fellow, 1969–1970.

(4) A. M. Aguiar, K. C. Hansen, and G. S. Reddy, *J. Amer. Chem. Soc.*, **89**, 3087 (1967).

(5) A. M. Aguiar and K. C. Hansen, *ibid.*, **89**, 4235 (1967).

(6) A. M. Aguiar, J. R. S. Irelan, G. W. Prejean, J. P. John, and C. J. Morrow, *J. Org. Chem.*, **34**, 2681 (1969).

(7) A. M. Aguiar, J. R. Irelan, C. J. Morrow, J. P. John, and G. W. Prejean, *ibid.*, **34**, 2684 (1969).

(8) A. M. Aguiar, G. W. Prejean, J. R. S. Irelan, and C. J. Morrow, *ibid.*, **34**, 4024 (1969).

(9) R. Majeste and L. M. Trefonas, *J. Heterocycl. Chem.*, **6**, 269 (1969).

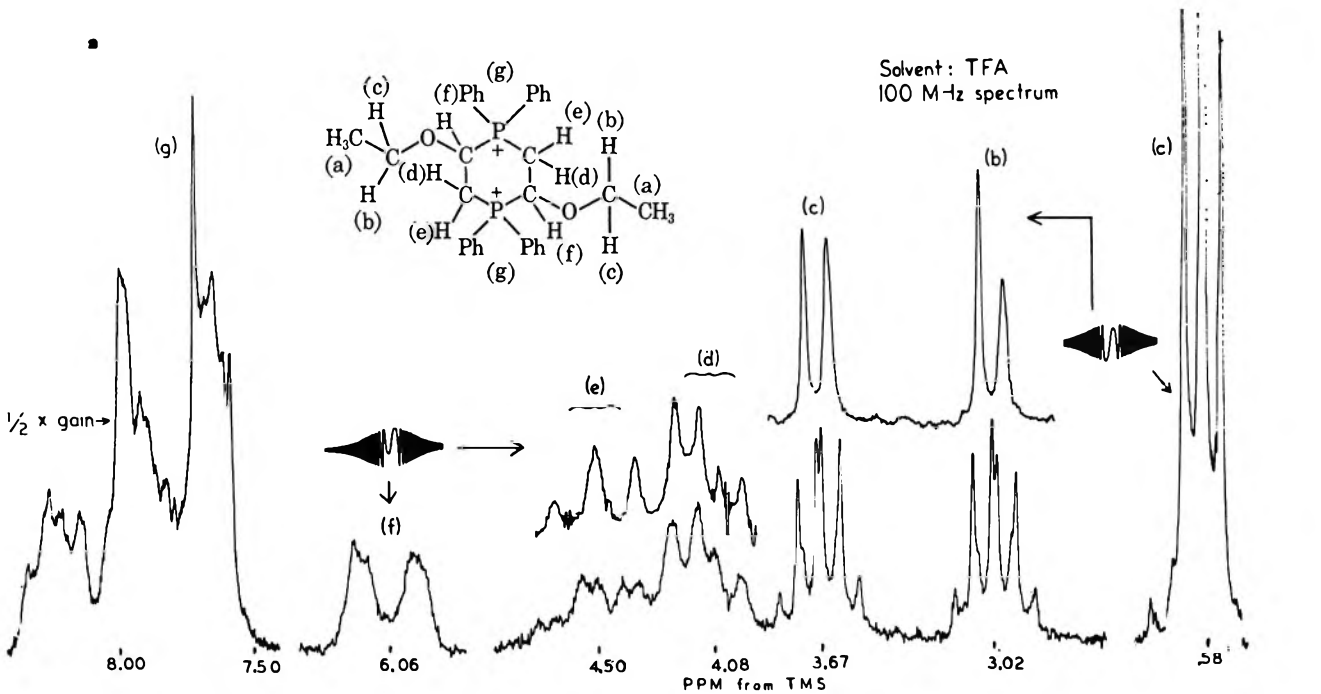


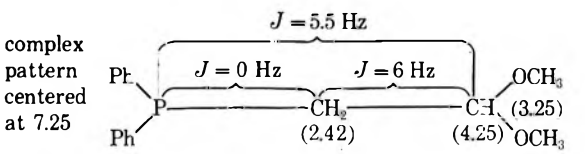
Figure 1.

representing 20 protons is ascribed to the hydrogen atoms of the four phenyl rings. The (6 H) triplet at $\delta = 0.58$ and the almost identical (4 H) multiplets at $\delta = 3.02$ and 3.67 are assigned to the methyl and nonequivalent methylene protons, respectively, of the ethoxy groups at C-2 and C-5. The nonequivalence of the methylene protons and the unusually high-field chemical shift of the methyl protons is attributed to the anisotropic effects of the phenyl groups located on the phosphorus atoms. The slightly broadened doublet (16 Hz) of doublets (9 Hz) at $\delta = 4.08$ (labeled D in the nmr spectrum) and a doubled (5 Hz) triplet (16 Hz) at $\delta = 4.50$ (labeled E) representing two protons each are assigned to the two nonequivalent methylene hydrogen atoms at C-3 and C-6. The 16-Hz splitting in the two resonances is due to the mutual geminal coupling between the two protons. The other large couplings of 9 and 16 Hz observed in the D and E resonances, respectively, are due to the spin interactions of the two protons with the phosphorus nuclei in the molecule. The small splittings of approximately 1.0 and 5.0 Hz present in the D and E absorptions are caused by the coupling of these two protons with the vicinal methine protons at C-2 and C-5, which resonate at $\delta = 6.06$ and are labeled F in the spectrum. This was confirmed when the broad doublet (20 Hz) of doublets (5 Hz) at $\delta = 6.06$ was irradiated in the frequency sweep mode of the 100-MHz spectrometer and the decoupled resonances of D and E at $\delta = 4.08$ and 4.50, respectively, were examined (see Figure 1). The magnitude of these spin couplings designated an equatorial orientation for F. The large coupling of 20 Hz observed in the resonance at $\delta = 6.06$ is due to the spin interaction of H-2 and H-5 with those of the phosphorus nuclei. By analogy, the proton labeled E is assigned an equatorial configuration from the magnitude of the PH coupling (16 Hz) seen in the resonance at $\delta = 4.50$. This assignment is in harmony with the observation that equatorial protons usually resonate downfield from their geminal axial neighbors.

Experimental Section

Diphenylphosphinoacetaldehyde Dimethyl Acetal (4a).—Lithium diphenylphosphide (made from 0.1 mol of diphenylphosphinous chloride and excess lithium) in tetrahydrofuran (THF) was added slowly to a stirred THF solution of 12.5 g (0.1 mol) of chloroacetaldehyde dimethyl acetal. An immediate, mildly exothermic reaction ensued with the decolorization of the lithium diphenylphosphide. The reaction mixture was stirred for 0.5 hr at room temperature. The THF was stripped off at reduced pressure and the residue was vacuum distilled yielding 20.3 g (74%) of a colorless liquid, bp 138–139° (0.2 mm).

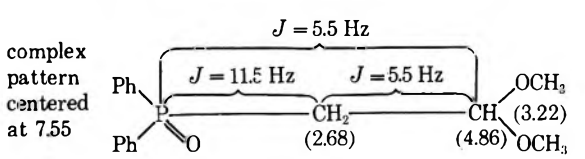
Nmr data for this compound, obtained in $CDCl_3$ solution at 60 MHz, were in good accord with this structure.



The above phosphine was characterized as the oxide by treatment of an acetone solution with 3% hydrogen peroxide. Evaporation of the acetone yielded an oil which crystallized upon drying, mp 111° (from cyclohexane). The ir spectrum showed strong phosphoryl absorption at 1180 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}O_3P$: C, 66.20; H, 6.55; P, 10.68. Found: C, 66.35; H, 6.63; P, 10.53.

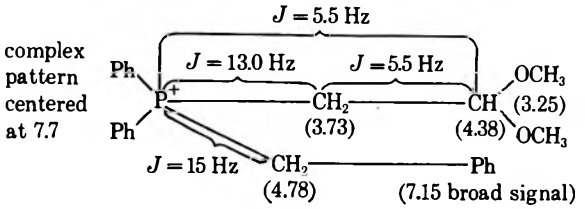
The nmr spectrum of this compound, obtained in $CDCl_3$ solution at 60 MHz, was in good accord with this structure.



The phosphine was further characterized as the benzyl bromide salt by reaction at room temperature with 1 equiv of benzyl bromide in dry benzene. A white solid precipitated, mp 163–164° (from ethyl acetate–methanol).

Anal. Calcd for $C_{23}H_{26}BrO_2P$: C, 62.06; H, 5.84. Calcd for $C_{23}H_{26}BrO_2P \cdot H_2O$: C, 59.65; H, 6.04. Found: C, 60.00, 59.97; H, 6.06, 5.92.

Nmr data for this compound, obtained in $CDCl_3$ solution at 60 MHz, were in good accord with this structure.



2,5-Dimethoxy-1,1,4,4-tetraphenyl-1,4-diphosphoniacyclohexane Dibromide (5a).—Diphenylphosphinoacetaldehyde dimethyl acetal (12.0 g, 0.047 mol) was dissolved in 200 ml of glacial acetic acid and this solution was brought to reflux. Hydrogen bromide was then passed slowly through the refluxing solution for 1 hr. The acetic acid was stripped off under reduced pressure and the residue was triturated with acetone yielding 9.1 g (50%) of a white solid, mp 208–210° dec (from acetonitrile–methanol).

Anal. Calcd for $C_{30}H_{32}Br_2O_2P_4$: C, 55.77; H, 4.95; Br, 24.70. Calcd for $C_{30}H_{32}Br_2O_2P_4 \cdot H_2O$: C, 54.26; H, 5.12; Br, 24.06. Found: C, 53.66; H, 4.94; Br, 24.50.

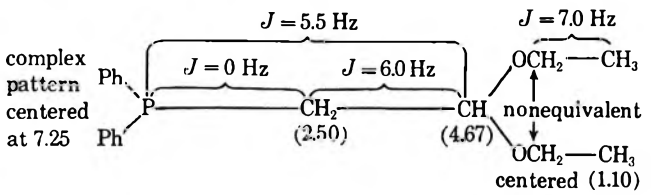
The dibromide was converted into a dipicrate by the metathetical reaction with sodium picrate in methanol yielding a yellow solid, mp 160° (from acetonitrile). Sodium fusion of a sample of the picrate gave a negative analysis for bromine.

Anal. Calcd for $C_{42}H_{36}N_6O_{16}P_2$: C, 53.53; H, 3.82; N, 8.91. Found: C, 52.56, 53.3; H, 3.39, 3.89; N, 8.72, 8.88.

Diphenylphosphinoacetaldehyde Diethyl Acetal (4b).—A tetrahydrofuran solution of 0.1 mol of lithium diphenylphosphide was added slowly with stirring over a period of 30 min to a solution of 15.3 g (0.1 mol) of chloroacetaldehyde diethyl acetal (Aldrich) in 100 ml of tetrahydrofuran. The reaction was not very exothermic and rather slow. The reaction mixture was stirred for 30 min at room temperature. The tetrahydrofuran was stripped off and the residue was vacuum distilled, yielding 20.8 g (69%) of **4b**, bp 163–165° (1.5 mm).

The infrared spectrum of a chloroform solution of **4b** showed no phosphoryl absorption between 8.0 and 9.0 μ.

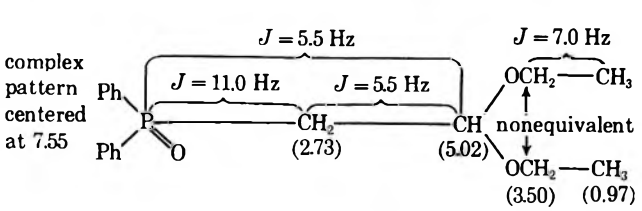
The nmr data for this compound, obtained in $CDCl_3$ solution at 60 MHz, were in good accord with this structure.



The above phosphine was characterized as the oxide by reaction of an acetone solution with 3% hydrogen peroxide in acetone. An exothermic reaction was noted, and evaporation of the solvent yielded a white crystalline solid, mp 101° (from hexane–cyclohexane).

Anal. Calcd for $C_{18}H_{23}O_3P$: C, 67.92; H, 7.23; P, 9.74. Found: C, 67.83; H, 7.01; P, 9.59.

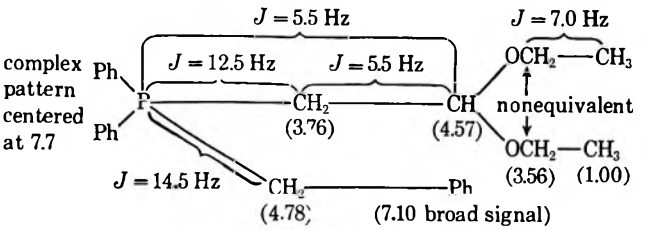
The nmr spectrum of this compound, obtained in $CDCl_3$ solution at 60 MHz, was in good accord with this structure.



The phosphine was further characterized as the benzylphosphonium bromide by reaction with excess benzyl bromide in benzene at reflux for 1 hr. The solid precipitate was recrystallized from ethyl acetate–methanol, mp 199–201°.

Anal. Calcd for $C_{25}H_{30}BrO_2P$: C, 63.42; H, 6.34; Br, 16.91; P, 6.55. Found: C, 63.56; H, 6.48; Br, 17.12; P, 6.53.

The nmr data for this compound, obtained in $CDCl_3$ solution at 60 MHz, were in good accord with this structure.



2,5-Diethoxy-1,1,4,4-tetraphenyldiphosphonia-1,4-cyclohexane Dibromide (5b).—Diphenylphosphinoacetaldehyde diethyl acetal (20 g, 0.066 mol) was dissolved in 150 ml of glacial acetic acid and hydrogen bromide was passed slowly through the solution at reflux for 2 hr and the solution allowed to stand at room temperature for 12 hr. The acetic acid was stripped off at reduced pressure and the residue was triturated with acetone yielding 13.5 g (61%) of **5b**, mp 208–210° (from acetonitrile–methanol).

Anal. Calcd for $C_{32}H_{36}Br_2O_2P_2 \cdot H_2O$: C, 55.49; H, 5.49; Br, 23.12. Found: C, 55.61; H, 5.68; Br, 23.16.

The infrared spectrum of a potassium bromide disk of **5b** showed absorptions at 6.98, 9.00, and 10.04 μ which are typical of aryl phosphonium salts. Strong absorption was also observed at 9.40 μ assigned to a carbon-to-oxygen single bond stretching frequency.

Picrate of 5b.—A sample of **5b** in methanol was mixed with an aqueous solution of sodium picrate and the immediate precipitation of a yellow solid resulted, mp 182–183° dec (from acetonitrile).

Anal. Calcd for $C_{44}H_{40}N_6O_{16}P_2$: C, 54.43; H, 4.12; N, 8.65; Br, 0.00. Found: C, 53.91; H, 3.73; N, 8.01; Br, 0.00.

Fluoroborate Salt of 5b.—A warm aqueous solution of **5b** and an aqueous solution of sodium fluoroborate were mixed and a white solid immediately precipitated, mp 260–262° (from ethyl acetate–methanol). The nmr spectrum of a trifluoroacetic acid solution of the fluoroborate salt was identical with that of the bromide.

Registry No.—**4a**, 24744-62-5; **4a** (oxide), 24744-63-6; **4a** (benzyl bromide salt), 24744-64-7; **4b**, 24744-65-8; **4b** (oxide), 24744-66-9; **4b** (benzyl bromide salt), 24744-67-0; **5a**, 24744-68-1; **5a** (dipicrate), 24744-69-2; **5b**, 24744-70-5; **5b** (picrate), 24799-52-8; **5b** (fluoroborate), 24806-55-1.

Acknowledgment.—We wish to acknowledge the National Science Foundation for Grant GP-7117, the National Institutes of Health for Grant GM AI 16828, the Petroleum Research Fund administered by the American Chemical Society for Grant 2326-A1,4, and the Robert A. Welch Foundation Grant V 314 (made to K. C. H.) for supporting this work.

^{19}F Nuclear Magnetic Resonance Spectra of Some Trifluoroacetanilides

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We have become interested in the transmission of electronic activation effects through the amide link from groups attached to the nitrogen atom to a reactive site on a carbon atom attached to the carbonyl

(1) NDEA Fellow, 1967–1968. Support from the Research Committee of the University of California is gratefully acknowledged.

group.[2] In addition to the study of rate effects, it was thought desirable to examine nonkinetic measurements of electronic effects in the amides.

Eight 4-substituted trifluoroacetanilides were prepared by reaction of the aniline with trifluoroacetic anhydride. The chemical shift of the fluorine resonance was measured in tetrahydrofuran solvent (5% concentration) at 56.4 MHz with trifluoroacetic acid as external standard.

The results are shown in Table I. The total spread

TABLE I
^{19}F CHEMICAL SHIFT OF 4-X-TRIFLUOROACETANILIDES

4 substituent	Registry no.	σ^+ [a]	Chemical shift[b]
OCH_3	332-34-3	−0.78	110.5
CH_3	350-96-9	−0.31	107.3
H	404-24-0	0	105.4
Br	24568-11-4	0.15	104.3
Cl	404-25-1	0.11	104.0
$COCH_3$	24568-13-6	0.50	104.2
$CO_2C_2H_5$	24568-14-7	0.48	103.0
NO_2	404-27-3	0.79	100.7

[a] Reference 5. [b] In Hz upfield from external trifluoroacetic acid, 0.021 *M* in tetrahydrofuran, 56.4 MHz.

of chemical shifts is less than 0.2 ppm. This value should be contrasted with the range of about 20 ppm obtained by Gutowsky[3] and Taft[4] for substituted fluorobenzenes and the range of about 2 ppm obtained for benzotrifluorides.[3] No measurements have been reported for trifluoroacetophenones. The present results indicate a very substantial compression of the chemical shift range in going from fluorobenzenes to trifluoroacetanilides. Within this narrow range, however, the ^{19}F chemical shifts of the acetanilides correlate well with Brown's σ^+ substituent constants.[5] The chemical shift for 4-acetyltrifluoroacetanilide is substantially removed from the best line, and the value for the 4-chloro compound shows minor deviation; these deviations have their parallels in measurements in the fluorobenzenes.[3] ρ for this set of data may be defined: $\rho = (a - a_0)/(a_0\sigma^+)$, where a is the chemical shift of substituted compound in Hz upfield from external trifluoroacetic acid, a_0 is the chemical shift of trifluoroacetanilide, and σ^+ is the constant associated with the substituent.[5] The value obtained is -0.058 ± 0.003, not including the acetyl value, or -0.054 ± 0.006, including the acetyl value.

It is clear that within the small range of chemical shifts reported a noninductive substituent effect is being observed. Several explanations such as resonance[6,7] or polarizability could adequately explain the observed data. The efficiency of transmission of electronic effects in the ^{19}F nmr chemical shifts of trifluoroacetanilides is substantially lower than that reported from reaction kinetics.[2] Presumably this difference reflects ground state *vs.* transition state sensitivity to substituent changes.

(2) H. W. Johnson, Jr., and M. Schweizer, *J. Org. Chem.*, **26**, 3666 (1961); H. W. Johnson, Jr., E. Ngo, R. C. Stafford, and Y. Iwata, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, No. ORGN 31; H. W. Johnson, Jr., E. Ngo, and V. A. Pena, *J. Org. Chem.*, **34**, 3271 (1969).

(3) H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Amer. Chem. Soc.*, **74**, 4809 (1952).

(4) R. W. Taft, *ibid.*, **79**, 1045 (1956); R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *ibid.*, **85**, 3146 (1963).

(5) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 285 (1957).

(6) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 281.

(7) P. Haake, W. B. Miller, and T. A. Tyssee, *J. Amer. Chem. Soc.*, **86**, 3577 (1964).

Experimental Section

The trifluoroacetanilides were synthesized from trifluoroacetic anhydride and the substituted aniline by standard methods.[8] Proton nmr spectra showed the usual pair of doublets ($J_{AB} \cong 9$ Hz) for the aromatic protons in a *para*-disubstituted benzene, and infrared spectra were consistent with the acetanilide structure. Melting point data follow: 4′ substituent (reported melting point, deg): $-OCH_3$, 113.5–114 (112.5–115);[8] $-CH_3$, 110–111 (111–112);[8] –H, 88–89 (88.5–90);[8] –Cl, 123–124 (123–124.5);[8] –Br,[9] 125.5–126; $-CO_2C_2H_5$,[9] 127.5–128.5; $-COCH_3$,[9] 160.5–161; $-NO_2$, 151.5–152.5 (151.5–153).[8]

Nmr spectra were measured in a Varian Associates HR spectrometer at 56.4 Mc at instrument temperature 35°; the instrument was equipped with the Varian superstabilizer. Frequency measurements were made by the audio side-band technique. Trifluoroacetic acid was used as the external standard and the trifluoroacetanilides were 2.1×10^{-2} *M* solutions in analytical reagent grade anhydrous tetrahydrofuran. The chemical shift of *p*-nitrotrifluoroacetanilide was measured as a function of concentration from 20 to 5% in THF; the fluorine resonance position changed 1 Hz in this concentration range. In some determinations *p*-nitrotrifluoroacetanilide was used as an internal standard; no appreciable difference between the internal and external standards was noted. Reproducibility (at least three measurements on each compound and ten measurements on the *p*-nitro derivative) was ±0.2 Hz.

(8) E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952).

(9) Satisfactory microanalysis (±0.3%) for this compound for C, H, and N were obtained from C. F. Geiger, 312 Yale St., Ontario, Calif. Melting points are uncorrected and were measured with a Thomas Unitemp bath.

Studies on the Antimicrobial Substances of Sponges. IV.[1a,b] Structure of a Bromine-Containing Compound from a Marine Sponge

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Received January 27, 1970

From a marine sponge *Verongia fistularis* and related species[3] we isolated four compounds: A, mp 195°; B, mp 191°; C, mp 132°; and D, mp 137°. The structure and synthesis of compound A, mp 195°, having a broad antibacterial spectrum, was reported in a recent paper.[4] A comparison of the ir, nmr, and mass spectra of compound C, molecular formula $C_{29}H_{50}O$, mp 132°, $[\alpha]^{20}D$ −38.7, with those of β-sitosterol[5] revealed them to be identical.

Now we wish to report the evidence leading to structure **1** for compound B, mp 191°. This compound was analyzed for $C_{10}H_{13}NO_4Br_2$ and showed infrared bands

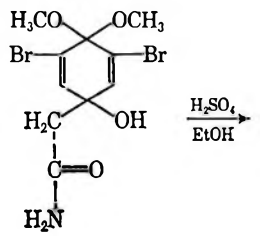
(1) (a) For part III in this series, see G. M. Sharma, B. Vig, and P. R. Burkholder, *Trans. Drugs Sea Symp., J. Ocean Technol.*, 119 (1968); (b) Lamont–Doherty Geological Observatory Contribution No. 1479.

(2) Postdoctoral research associate, 1967–1969.

(3) G. M. Sharma and P. R. Burkholder, *J. Antibiot.* (Tokyo), *Ser. A*, **20**, 200 (1967).

(4) G. M. Sharma and P. R. Burkholder, *Tetrahedron Lett.*, 4147 (1967).

(5) A pure sample of β-sitosterol was provided by Professor Maxwell S. Doty, University of Hawaii.



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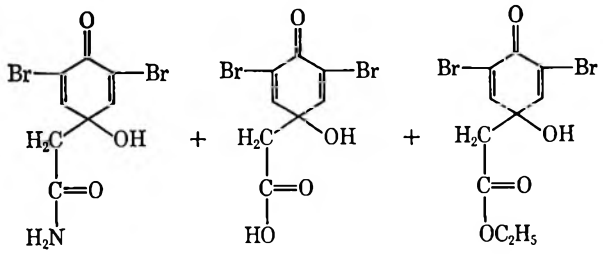
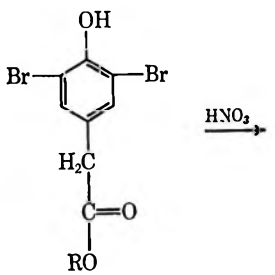
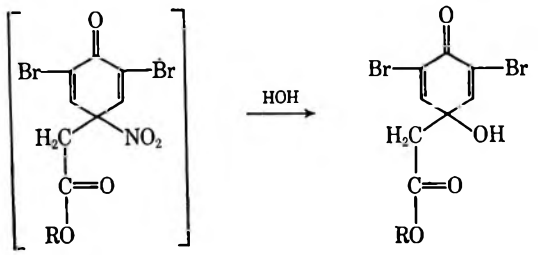
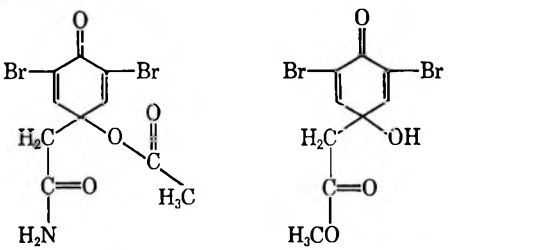


2 3 4



5a, R = H
b, R = C_2H_5



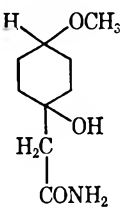


8 10

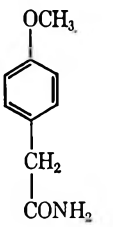
(KBr) at 3420, 3375, 3315, 1698, 1640 cm^{-1}, indicating the presence of hydroxyl group, amide function, and double bonds. The mass spectrum of this compound exhibited three weak molecular ion peaks at *m/e* 373, 371, 369, in the relative intensity ratio of 1:2:1, confirming the presence of two bromine atoms and the molecular weight corresponding to the formula stated above. Other prominent ions containing two bromine atoms occurred at *m/e* 342, 340, 338 (M − OCH_3); 324, 322, 320 [(M − OCH_3) − H_2O]; 315, 313, 311 (M − 58, loss of CH_2CONH_2). The presence of two methoxyl groups in the molecule was confirmed by functional group analysis. Formation of a mono-O-acetyl derivative indicated the presence of a single hydroxyl group.

Hydrolysis of B with sulfuric acid in ethanol produced three compounds having mp 195°, 192°, and 121°. The compound with mp 195° was confirmed to be dienone **2** by comparison with an authentic sample.[4] The other two products with mp 192° and 121° were assigned structures **3** and **4**, respectively, on the basis of spectral data. Further confirmation of these structures was obtained by their direct synthesis. Compounds **3** and **4** were synthesized by treating 4-hydroxy-3,5-dibromophenyl acetic acid **5a** and its ethyl ester **5b** with nitric acid.[4,6] It was later discovered that B could be quantitatively converted into **2** by heating with 70% acetic acid for 2 hr. Formation of dienone **2** from the compound B on acid hydrolysis supports the assignment of structure **1** for the latter.

On catalytic hydrogenation **1** absorbed 5.5 mol of hydrogen to furnish a mixture of products from which only one compound, mp 137°, could be obtained in an analytically pure state. On the basis of spectroscopic evidence (ir, nmr, and mass spectra) we have assigned structure **6** for this compound.



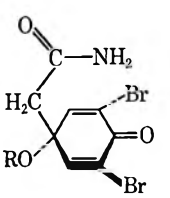
6



7

Since the total hydrogenation product showed aromatic absorption in the uv at 275 and 285 mμ, the presence of the expected product *p*-methoxyphenylacetamide **7** in the mixture was indicated, but this compound could not be isolated in the pure state.

The nuclear magnetic resonance spectrum[7] of B is fully in accord with the proposed structure **1**. In the nmr spectrum of the dienone **2** and of its acetyl derivative **8**, the protons attached to the amide nitrogen were found to resonate[4] at *ca.* 2.97 ppm instead of the expected values of 8 to 5 ppm. The marked excess shielding of the amide protons in **2** and **8** may be explained on the basis of the folded conformation **9**. In this con-



9

formation, the amide group will not only be in the shielding zone of the dienone ring but may also be prevented from making intermolecular hydrogen bonds. Both these effects acting in concert may shift the amide resonance to the observed high-field position.

The amide group in the acetate of **1** also exhibits the unusual chemical shift (3.25 ppm) although no dienone moiety is present. It would seem, therefore, that the acetoxy group may also play a significant role in the shielding of the amide protons. Single crystal X-ray

(6) E. Muller, A. Shick, and K. Scheffler, *Chem. Ber.*, **92**, 474 (1959).
(7) Spectral data are recorded in the Experimental Section.

diffraction analyses of these compounds are being performed to check the validity of the above interpretations.

As the compounds **1** and **2** were isolated from the sponge by extraction with methanol, the possibility was considered that the former compound might have been obtained from the latter during isolation procedure. However, failure to convert **2** into **1** by reacting with methanol under various conditions supports the view that **1** is indeed a naturally occurring compound. Reaction of **2** with methyl orthoformate also failed to produce the acetal **1**.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Ultraviolet spectra were determined on a Beckman Model DK2A recording spectrophotometer and infrared spectra on a Model 337 Perkin-Elmer spectrophotometer; nuclear magnetic resonance spectra were determined on a Varian A-60A spectrometer in deuterated acetone (unless otherwise stated) using tetramethylsilane as internal standard. Microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium im Max-Planck-Institut fur Kohlenforschung, 433 Mulheim (Ruhr), West Germany.

Isolation of 1.—The isolation of **1** from sponge *Verongia fistularis* has been described in a previous paper.[3] The molecular formula $C_{10}H_{15}NO_4Br_2$ reported in that publication is now revised to $C_{10}H_{13}NO_4Br_2$ on the basis of more accurate combustion analysis of a sample prepared by crystallizing three times from ethyl acetate to afford colorless prisms: mp 191°; ir (KBr) 3420, 3375, 3315, 1698 (amide C=O), 1640 cm^{-1}; nmr δ 6.75 (a singlet over a very broad amide resonance, 4 H, amide and olefinic protons, after addition of D_2O, 2 H), 5.75 (s, 1 H, OH), 3.04 and 3.06 (two singlets, 6 H, two OCH_3), and 2.56 (s, 2 H, CH_2—$CONH_2$).

Anal. Calcd for $C_{10}H_{13}NO_4Br_2$: C, 32.34; H, 3.5; N, 3.77; Br, 43.12; OCH_3, 16.71. Found: C, 32.18; H, 3.65; N, 3.79; OCH_3, 16.54.

Acetylation of 1.—Acetic anhydride (0.5 ml) was added to a solution of **1** (100 mg) in anhydrous pyridine. After 12 hr at 20°, the reaction mixture was worked up to give, after three crystallizations from ethyl acetate, fine colorless needles (60 mg): mp 184°; ir (KBr) 3460 (NH_2 of amide group), 1720 (ester C=O), and 1698 cm^{-1} (amide C=O); nmr δ 7.1 (s, 2 H, olefinic protons), 3.15 and 3.25 (two singlets, 8 H, two OCH_3 and $CONH_2$, after addition of D_2O, 6 H), 2.92 (s, 2 H, CH_2—CO), and 2.05 (s, 3 H, CH_3COO). Actually the $CONH_2$ resonance was found to shift between 2.95 and 3.2 ppm.

Hydrolysis of 1 with Sulfuric Acid.—To a solution of **1** (1.05 g) in ethanol (10.0 ml) was added 10% sulfuric acid (40 ml), and the reaction mixture was heated on a boiling water bath for 1 hr. The solution was cooled and 6 ml of 28% ammonium hydroxide solution was added. Approximately half the solvent was removed under reduced pressure and the remaining solution was extracted three times with ethyl acetate. The ethyl acetate extract after drying and evaporation gave a semisolid residue (800 mg) which was chromatographed over silica gel. Continuous elution with ether–benzene mixture ratio (1:4) first gave the ester **4** (38 mg, mp 121°) and then the acid **3** (295 mg, mp 195–196°). The structure of these compounds was established by synthesis from ethyl 4-hydroxy-3,5-dibromophenylacetate **5b** and the corresponding acid **5a**. Elemental analysis and spectral data are given later (**Synthesis of Dienones 3 and 4**).

Further eluting the column with ethyl acetate gave dienone **2**, mp 195°, identical with authentic[4] **2**.

Hydrolysis of 1 with Dilute Acetic Acid.—A solution of **1** (1.036 g) in acetic acid (14 ml) and water (7 ml) was heated for 2 hr on a boiling water bath. The solvent was removed under reduced pressure and the residue crystallized from ethyl acetate or water to give dienone **2** (600 mg), mp 195°.

Preparation of 4-Hydroxy-3,5-dibromophenylacetic Acid (5a).—A solution of *p*-hydroxyphenylacetic acid (7.6 g) in glacial acetic acid (250 ml) was stirred mechanically and bromine (16.5 g) dissolved in 5 ml of acetic acid was added dropwise over a period of 30 min. The bromination was allowed to proceed at room temperature for 72 hr. The solvent was then removed under reduced pressure, and the residue crystallized from water to afford pure **5a** (10 g): mp 195–196°; uv max (MeOH) 282 mμ (ϵ 2700) and 287 (2600); ir (KBr) 3350 (broad OH), 1650 cm^{-1} (-C=O); nmr δ 9 (broad OH), 7.5 (s, 2 H, aromatic protons), and 3.64 (s, 2 H, CH_2—C=O).

Anal. Calcd for $C_8H_6O_3Br_2$: C, 30.96; H, 1.93; Br, 51.61. Found: C, 31.01; H, 2.1; Br, 51.53.

Preparation of Ethyl 4-Hydroxy-3,5-dibromophenylacetate (5b).—This ester was prepared by refluxing (using Dean and Stark apparatus to remove water) a mixture of **5a** (2 g), ethanol (50 ml), benzene (125 ml), and concentrated sulfuric acid (0.5 ml) for 8 hr. The reaction mixture was cooled and diluted with water. The benzene layer was washed with sodium carbonate solution, dried, and evaporated to give ester **4**, 1.98 g (96%). Two crystallizations from hexane gave an analytical sample, mp 105°.

Anal. Calcd for $C_{10}H_{10}O_3Br_2$: C, 33.90; H, 2.80; Br, 45.19. Found: C, 38.81; H, 2.90; Br, 45.33.

Synthesis of Dienones 3 and 4.—A mixture of concentrated nitric acid and glacial acetic acid (1:9 v/v) was cooled to 10° and used for the syntheses of dienones **3** and **4** as described below.

A measured volume (2.1 ml) of the nitric acid–acetic acid mixture was added to a stirred solution of **5a** (330 mg) in glacial acetic acid (3 ml) at 10°. After stirring for 3 hr, the nitric acid was neutralized by adding sodium bicarbonate (600 mg), and the solvent was stripped off the reaction mixture under reduced pressure. The residue was suspended in water (10 ml) and extracted with ethyl acetate. The ethyl acetate extract was dried and evaporated to give a brown residue (250 mg). Chromatography of this material on silica gel and elution with ether–benzene mixture (1:4) gave pure dienone **3** (180 mg). Crystallization from ethyl acetate gave a white solid: mp 195–196°; uv max (MeOH) 255 mμ (ϵ 8600); ir (Nujol) 3475 (OH), 1700 (carboxylic C=O), 1670, 1600 cm^{-1} (dienone C=O); nmr δ 7.6 (s, 2 H, olefinic protons), 6.0 (broad, 2 H, exchanges with D_2O), and 2.88 (s, 2 H, -CH_2—CO_2H).

Anal. Calcd for $C_8H_6O_4Br_2$: C, 29.4; H, 1.84; Nr, 49.08. Found: C, 29.61; H, 1.98; Br, 49.38.

The dienone **4** was synthesized in 76% yield by reacting **5b** with nitric acid–acetic acid mixture in the manner described above. The ethyl acetate extract was evaporated to give a residue which was crystallized from hexane to afford pure **4** as colorless needles: mp 121°; uv max (MeOH) 253 mμ (ϵ 8632); ir (Nujol) 3460 (OH), 1720 (ester C=O), and 1680 cm^{-1} (dienone C=O); nmr ($CDCl_3$) δ 7.42 (s, 2 H, olefinic protons), 4.24 (quartet, 2 H, O—CH_2·CH_3), 2.78 (s, 2 H, CH_2—C=O), and 1.28 (t, 3 H, O—CH_2·CH_3).

Anal. Calcd for $C_{10}H_{10}O_4Br_2$: C, 33.9; H, 2.82; Br, 45.19. Found: C, 33.81; H, 2.90; Br, 45.33.

Catalytic Hydrogenation of 1.—A mixture of **1** (556 mg), sodium acetate (400 mg), and 10% Pd-C (80 mg) in methanol (50 ml) was hydrogenated. After 1.5 hr the absorption of the hydrogen had stopped and approximately 5 mol equiv of hydrogen had been consumed. The reaction mixture was filtered and evaporated to give a white residue. Water was added to the residue and the aqueous suspension was extracted with ethyl acetate. The ethyl acetate extract was dried and evaporated to give a mixture (280 mg) which could not be separated into its components by column chromatography or preparative tlc. Since the total hydrogenation product showed uv absorption at 275 and 285 mμ, the presence of *p*-methoxyphenylacetamide **7** was indicated.

The hydrogenation product was heated with benzene (4 ml) and the insoluble material was collected by suction. The insoluble compound was crystallized four times from ethyl acetate to give **6** (25 mg): mp 137°; uv max (MeOH) only end absorption; ir (KBr) 3525, 3310 (OH, $CONH_2$), 3000, 2950 (methylenes), and 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 6.15 (broad, 2 H, $CONH_2$), 3.75 (m, 1 H), 3.4 (s, 3 H, OCH_3), 2.4 (s, 2 H, CH_2—CO), 1.7 (broad envelope, 9 H, methylenes of cyclohexane and OH); mass spectrum (70 eV) *m/e* 187 (M^+) is not observed, 169 (M − 18), 153, 122 (150 − OCH_3).

Anal. Calcd for $C_9H_{17}O_3N$: C, 57.75; H, 9.09; N, 7.48. Found: C, 57.66; H, 9.04; N, 7.53.

Attempted Synthesis of 1 from 2.—(a) The dienone **2** (100 mg) was dissolved in anhydrous methanol (10 ml), and the solution was kept at room temperature for 2 days. Examination of the uv and nmr spectra indicated the absence of **1** in the reaction mixture.

(b) To a solution of dienone **2** (100 mg) in anhydrous methanol, a catalytic amount of *p*-toluenesulfonic acid (10 mg) was added and the reaction mixture refluxed for 24 hr. Removal of solvent gave 105 mg of a material which was dissolved in ethyl acetate and washed with water. The ethyl acetate extract was dried and evaporated to give a semisolid (100 mg). Uv and nmr spectra of this material indicated the absence of **1**. The nmr spectrum instead indicated the presence of dienone **10**. Chromatography over silica gel gave pure **10** (25 mg, liquid) on elution with ether–benzene mixture (1:4). Further eluting the column with ethyl acetate gave the starting material, dienone **4**.

For combustion analysis the solid acetyl derivative of **10** was prepared. The acetyl derivative was crystallized from hexane to give colorless needles: mp 140°; uv max (MeOH) 258 mμ (ε 8420).

Anal. Calcd for $C_{11}H_{10}O_5Br_2$: C, 34.55; H, 2.61; Br, 41.88. Found: C, 34.74; H, 2.59; Br, 41.50.

(c) The dienone **2** was treated with methyl orthoformate using the conditions reported in literature.[8] Spectroscopic identification of the reaction product failed to reveal the presence of acetal **1**.

Registry No.—**1**, 24742-01-6; **1** (acetate), 24742-02-7; **3**, 24742-03-8; **4**, 24744-57-8; **5a**, 24744-58-9; **5b**, 24744-59-0; **6**, 24744-60-3; **10** (acetate), 24744-61-4.

Acknowledgment.—This work has been supported in part by National Institutes of Health Grant GM-11735 and in part by Sea Grant Project GH-16.

(8) L. F. Feiser and M. Feiser in "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, N. Y., 1967, pp 1206–1207.

Synthesis of Secondary Amines *via* Triphenylphosphinimines

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In continuation of our investigation utilizing triphenylphosphinimines (I) as tools in organic and inorganic synthesis,[2a–c] we investigated further the use of I in the preparation of mixed secondary amines. Our attention was mainly directed toward (a) the synthesis of secondary amines containing a cycloalkyl group and (b) establishing the scope and limitations of this method for the preparation of such amines. The synthesis followed the sequence of reactions of eq 1 and 2.

$$Ph_3\overset{+}{P}\text{–}\overset{-}{N}R \longleftrightarrow Ph_3P{=}NR + R'X \longrightarrow [Ph_3P\text{–}NRR']^+X^- \quad (1)$$

$$[Ph_3PNRR']^+X^- \xrightarrow{H_2O} Ph_3P{=}O + HNRR'^+X^- \quad (2)$$

R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *t*-Bu, 1-Adamantyl
R′ = Me, Et; X = I, Cl, Br

No difficulties were encountered in preparing the corresponding I with R = cyclopropyl, -pentyl, -hexyl, -heptyl, and adamantyl. However, again as reported previously,[2a] only MeI and EtI could be added according to eq 1. Use of any higher alkyl groups, including cyclopropyl, resulted in HX elimination from the alkyl halide and yielded alkylaminotriphenylphosphonium halides according to eq 3.

$$Ph_3P{=}NR + R'X \longrightarrow [Ph_3P\text{–}NHR]^+X^- + \text{olefin}^{2d} \quad (3)$$

R′ = any C_3 and higher alkyl; X = I

Alkylaminotriphenylphosphonium halides needed for the preparation of I were obtained by treating triphenyldibromophosphorane with the corresponding alkylamine in the presence of triethylamine.[2a,3] Dehydrohalogenation of these phosphonium salts was easily accomplished by treatment with sodium amide in liquid ammonia.[2a] The resulting triphenylphosphinecycloalkylimines were very sensitive to moisture and were used without further purification for the subsequent syntheses. These were carried out according to eq 1 by refluxing the corresponding triphenylphosphinimines in excess alkyl halide. Data on the resulting compounds are compiled in Table I.

All the dialkylaminophosphonium iodides obtained could be hydrolyzed as shown in eq 2. The mixed secondary amines were formed in good yields and were characterized as hemioxalates. Pertinent data are reported in Table II.

In conclusion it can be stated that alkyl addition to triphenylalkylphosphinimines, to give after hydrolysis mixed secondary amines, is limited to addition of methyl and ethyl groups.

Experimental Section

Melting points are uncorrected. Microanalysis was performed by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim/Ruhr, Germany, and by Galbraith Laboratories, Knoxville, Tenn.

Cycloalkylaminotriphenylphosphonium Bromides.—To an ice-cooled suspension of triphenyldibromophosphorane (0.1 mol) in benzene was slowly added a solution of triethylamine (0.1 mol) and the appropriate cycloalkylamine (0.1 mol) in 50 ml of dry benzene. The reaction was stirred for 3 hr before filtering. The collected precipitate was washed with ether and then with ice water. After drying it was dissolved in 100 ml of chloroform, treated with Norit, and filtered. Excess anhydrous ether (200 ml) was added to the chloroform solution and the precipitated bromide was filtered off. The mother liquors yielded a second crop on refrigerating overnight. The cycloalkylaminotriphenylphosphonium bromides were recrystallized from chloroform–ether to give analytically pure samples.

Cyclopropylaminotriphenylphosphonium bromide: yield 82%; mp 204°. *Anal.* Calcd for $C_{21}H_{21}BrNP$: C, 63.31; H, 5.31; N, 3.52. Found: C, 63.10, H, 5.34; N, 3.50.

Cyclopentylaminotriphenylphosphonium bromide: yield 89%; mp 188°. *Anal.* Calcd for $C_{23}H_{25}BrNP$: C, 64.79; H, 5.91; N, 3.29. Found: C, 65.27; H, 5.96; N, 3.35.

Cycloheptylaminotriphenylphosphonium bromide: yield 85%; mp 194–195°. *Anal.* Calcd for $C_{25}H_{29}BrNP$: C, 66.07; H, 6.43; N, 3.08. Found: C, 66.14; H, 6.22; N, 3.24.

Adamantylaminotriphenylphosphonium Bromide: yield 79%; mp 261–263°. *Anal.* Calcd for $C_{28}H_{31}BrNP$: N, 6.30. Found: N, 6.32.

Triphenylphosphinecycloalkylimines.—To a stirred suspension of the appropriate cycloalkylaminotriphenylphosphonium bromide (0.05 mol) in anhydrous ammonia was added 2.2 g of sodium amide (0.055 mol) and the resulting mixture was stirred for 1 hr in a Dry Ice–acetone bath. Ammonia was then evaporated by removing the cold bath and continuing the stirring. The solid remaining in the flask was extracted repeatedly with anhydrous ether. Evaporation of the combined extracts gave the desired phosphinimines which were recrystallized from anhy-

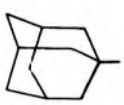
(1) M. Jayawant, Ph.D. Thesis, University of Cincinnati, Cincinnati, Ohio, 1967, and P. Gutsch, 1970, respectively.

(2) (a) H. Zimmer and G. Singh, *J. Org. Chem.*, **28**, 483 (1963); (b) H. Zimmer and G. Singh, *Angew. Chem., Int. Ed. Engl.*, **2**, 395 (1963); (c) H. Zimmer and G. Singh, *J. Org. Chem.*, **29**, 3412 (1964). (d) The olefins were qualitatively identified by decolorization of bromine–water reagent. The stoichiometry and exact mechanism of the olefin forming reaction are presently being investigated.

(3) L. Horner and H. Hoffmann, *Angew. Chem.*, **68**, 473 (1956).

TABLE I

$$[(C_6H_5)_3P{=}NR + R'I \longrightarrow \left[(C_6H_5)_3P{-}N\begin{matrix}R'\\R\end{matrix}\right]^+ I^-$$ [a]

Compd no.	R	R′	Formula	Mol wt	Mp,[b] °C	Yield, %	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1		CH_3	$C_{22}H_{23}INP$	459.29	211–212	85.7	57.51	57.47	5.05	5.06	3.05	30.4
2		C_2H_5	$C_{23}H_{25}INP$	473.32	234–235	78.2	58.34	57.69	5.32	5.19	2.96	3.01
3		CH_3	$C_{24}H_{27}INP$	487.35	234–235	87.5	59.16	59.05	5.59	5.60	2.87	3.01
4		C_2H_5	$C_{25}H_{29}INP$	501.37	183–184	75.6	59.84	59.23	5.83	5.66	2.79	3.06
5		CH_3	$C_{25}H_{29}INP$	501.37	248–249	78.2	59.84	59.98	5.83	5.54	2.79	2.78
6		C_2H_5	$C_{26}H_{31}INP$	515.42	186–187	70.0	60.59	60.91	6.06	5.84	2.72	2.84
7		CH_3	$C_{26}H_{31}INP$	515.42	237–238	75.4	60.59	60.01	6.06	6.13	2.72	2.91
8		C_2H_5	$C_{27}H_{33}INP$	529.44	201–202	68.3	61.25	61.25	6.28	6.14	2.64	2.20
9		CH_3	$C_{29}H_{33}INP$	553.46	271–272	95.5	62.95	63.03	5.97	6.35	2.54	2.59

[a] Crystallized from $CHCl_3$–ether. [b] Melting points are uncorrected.

TABLE II

$$\left[(C_6H_5)_3\overset{+}{P}{-}N\begin{matrix}R\\R'\end{matrix}\right]^+ I^- \xrightarrow[2.\ \text{anhydrous (COOH)}_2]{1.\ \text{alcoholic KOH}} [RR'NH_2]^+[OOC{-}COOH]^-$$

Compd no.	R	R′	Formula	Mol wt	Yield,[a] %	Mp,[b] °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1		CH_3	$C_6H_{11}NO_4$	161.16	76.3	110–111	44.71	44.77	6.88	7.12	8.69	8.74
2		C_2H_5	$C_7H_{13}NO_4$	175.18	74.0	169–170	47.99	48.04	7.48	7.61	8.00	8.11
3		CH_3	$C_8H_{15}NO_4$	189.21	68.7	119.5–120.5	50.78	50.65	7.99	8.17	7.40	7.40
4		C_2H_5	$C_9H_{17}NO_4$	203.23	71.8	137–138	53.19	53.06	8.43	8.38	6.89	7.10
5		CH_3	$C_9H_{17}NO_4$	203.23	65.5	107.5–108.5	53.19	53.03	8.43	8.17	6.89	7.00
6		C_2H_5	$C_{10}H_{19}NO_4$	217.26	68.6	161–162	55.28	55.64	8.82	8.42	6.45	6.44
7		CH_3	$C_{10}H_{19}NO_4$	217.26	67.0	157–158	55.23	55.38	8.82	8.84	6.45	6.44
8		C_2H_5	$C_{11}H_{21}NO_4$[c]	231.29	69.4	171.5–172.5	57.12	56.92	9.15	8.89	6.06	6.30
9		CH_3	$C_{24}H_{40}N_2O_4$[d] $\times$ ½ H_2O	429.58	82.0	221 (d)	67.10	67.25	9.56	9.60	6.53	6.44

[a] Crystallized from ethanol–ether. [b] Melting points are uncorrected. [c] Crystallized from 95% ethanol as hemihydrate. [d] Crystallized as $[RR'NH_2)_2{}^+[OOCCOO]^{2-}\cdot{}^1/_2\ H_2O$

drous hexane. It is mandatory to keep an inert and dry atmosphere over solutions or solids during reactions, isolations, and crystallization.

The crude solids were usually used directly without further purification. The crude phosphinimines could be stored over KOH pellets in a vacuum desiccator without appreciable decomposition.

N-Methylcyclyalkylaminotriphenylphosphonium Iodides (Table I, Compounds 1, 3, 5, 7).—The appropriate triphenylphosphinecycloalkylimine (3–4 g) and 15 ml of methyl iodide were refluxed in an inert atmosphere for 3 hr. To the solution, after cooling, was added sufficient anhydrous ether, whereupon a pale yellow precipitate was deposited. Purification was done by crystallization from chloroform–ether. Yields based on starting phosphinimine were usually high (Table I).

N-Ethylcycloalkylaminotriphenylphosphonium Iodides (Table I, Compounds 2, 4, 6, 8).—These compounds were obtained analogously except that 15 ml of anhydrous *t*-butyl alcohol was used as solvent.

N-Methylcycloalkyl- and N-Ethylcycloalkylammonium Hemioxalates. Hydrolysis of N-Methylcycloalkyl- and N-Ethylcycloalkylaminotriphenylphosphonium Iodides (Table II, Compounds 1–8).—A mixture of 3 g of the appropriate dialkylaminotriphenylphosphonium iodide (*ca.* 0.0055–0.007 mol) and 30 ml of 2% alcoholic potassium hydroxide solution was sealed under an inert atmosphere in a Jena glass pressure bottle and was heated on a steam bath for 3 hr. The bottle then was chilled and carefully opened. The reaction mixture which contained the free amine was saturated with NaCl and was extracted with ether. After combining all ether extracts and drying them over anhydrous sodium sulfate, they were filtered slowly with stirring into a solution of 2 g of anhydrous oxalic acid in 75 ml of dry ether. The white precipitate of hemioxalate which immediately formed was collected, washed with anhydrous ether, and finally purified by recrystallization from ethanol–ether.

Registry No.—Cyclopropylaminotriphenylphosphonium bromide, 24571-65-1; cyclopentylaminotriphenylphosphonium bromide, 24571-66-2; cycloheptylaminotriphenylphosphonium bromide, 24571-67-3; adamantylaminotriphenylphosphonium bromide, 24571-68-4; Table I—**1**, 24571-69-5; **2**, 24571-70-8; **3**, 24571-71-9; **4**, 24571-72-0; **5**, 24571-73-1; **6**, 24571-74-2; **7**, 24571-75-3; **8**, 24571-76-4; **9**, 24571-77-5; Table II—**1**, 24571-78-6; **2**, 24571-79-7; **3**, 24571-80-0; **4**, 24571-81-1; **5**, 24571-82-2; **6**, 24571-83-3; **7**, 24571-84-4; **8**, 24571-85-5; **9**, 24571-86-6.

Acknowledgment.—Partial financial support of this research through the U. S. Army Research Office, Grant DA-ARO-D-31-124-G122, and the National Institutes of Health, Grant CY-5841, is gratefully acknowledged.

Photodimerization of Some Thiophene Analogs of Chalcone

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Since the early work of Stobbe[1,2] concerning the photodimerization of chalcone (benzalacetophenone) and some of its derivatives, this reaction has attracted surprisingly little attention.[3] Recently[4] we established that 1,2-dithienylethenes and 2-styrylthiophene, in contrast to stilbene,[5] failed to undergo photochemical dimerization.[4] It seemed of interest to see if the replacement of a phenyl by a thienyl ring in chalcone would also prevent dimerization. An additional motivation was provided by the fact that dimerization would yield cyclobutanes substituted with thiophene rings. This in turn would open the way to the synthesis of unusual cyclobutanes.[6]

Results

The heterocyclic chalcones **1–3** were readily prepared by the condensation of the appropriate aldehydes and ketones as described in literature.[7]

Concentrated solutions (*ca.* 35% wt/vol) in chloroform were irradiated in ordinary micro test tubes for 20 hr using 350 mμ ("dark light") lamps. In addition to large amounts of resinous material, insoluble in ethanol, colorless soluble compounds which turned out to be the cyclodimers **5–8** were also formed. 3-Phenyl-1-(2-thienyl)-2-propen-1-one (**1**) under the given conditions afforded the dimer **5** in 10% yield, mp 128–129.5° (from ethanol). Similarly, 1-phenyl-3-(2-thienyl)-2-propen-1-one (**2**) gave the cyclobutane derivative **6**, mp 132–134° (from ethanol) in 6–10% yield; 1,3-di-2-thienyl-2-propen-1-one (**3**) furnished in 4% yield a mixture of dimers **7** and **8**, mp 124–134° (from ethanol), in a ratio of about 10:1. The dimeric structure of the compounds was revealed by elemental analysis in combination with molecular weight determinations (osmometric in carbon tetrachloride) and by the spectroscopic properties. In order to elucidate the stereochemistry of the dimers the experiments of Stobbe[1,2] were repeated. Irradiation of a concentrated solution of 1,3-diphenyl-2-propen-1-one (chalcone, **4**) in chloroform in small quartz tubes for 20 hr afforded in 6% yield the dimer **9**, mp 125–126.5° (from ethanol, lit.[2] 124–125°). The reaction was incomplete, however, since considerable starting material remained (as a *cis–trans* mixture) and no resinous polymer was found. When ordinary glass tubes were used, another dimer was formed in extremely low yield upon irradiation of a solution of chalcone for 20 hr. Almost all of the starting material was still present as a *cis–trans* mixture. This dimer **10** (mp 234–236°) was also reported by Stobbe. The dimerizations of **1** and **4** have also been carried out in the presence of iodine, taking longer irradiation times (*ca.* 48 hr). The yields were improved considerably by this procedure; **1** gave a 22% yield of **5**, while **4** furnished the dimer **9** in 28% yield (Scheme I).

Discussion

On inspection of the mass spectra of the photodimers **5** and **6**, it was found that the fragmentation pattern was compatible only with a head-to-head structure.

(1) H. Stobbe and A. Hensel, *Ber.*, **59**, 2254 (1926).

(2) H. Stobbe and K. Bremer, *J. Prakt. Chem.*, **123** [2], 1 (1929).

(3) We noted only the dimerization of nitrochalcones: I. Tărăsescu and F. Hudosan, *Acad. Repub. Pop. Rom., Bul. Stiint., Sect. Stiinte Technice Chim.*, **5**, 37 (1953); *Chem. Abstr.*, **50**, 14628 (1956); *Rev. Chim., Acad. Repub. Pop. Rom.*, **1** (2), 39 (1956); *Chem. Abstr.*, **52**, 2817 (1958).

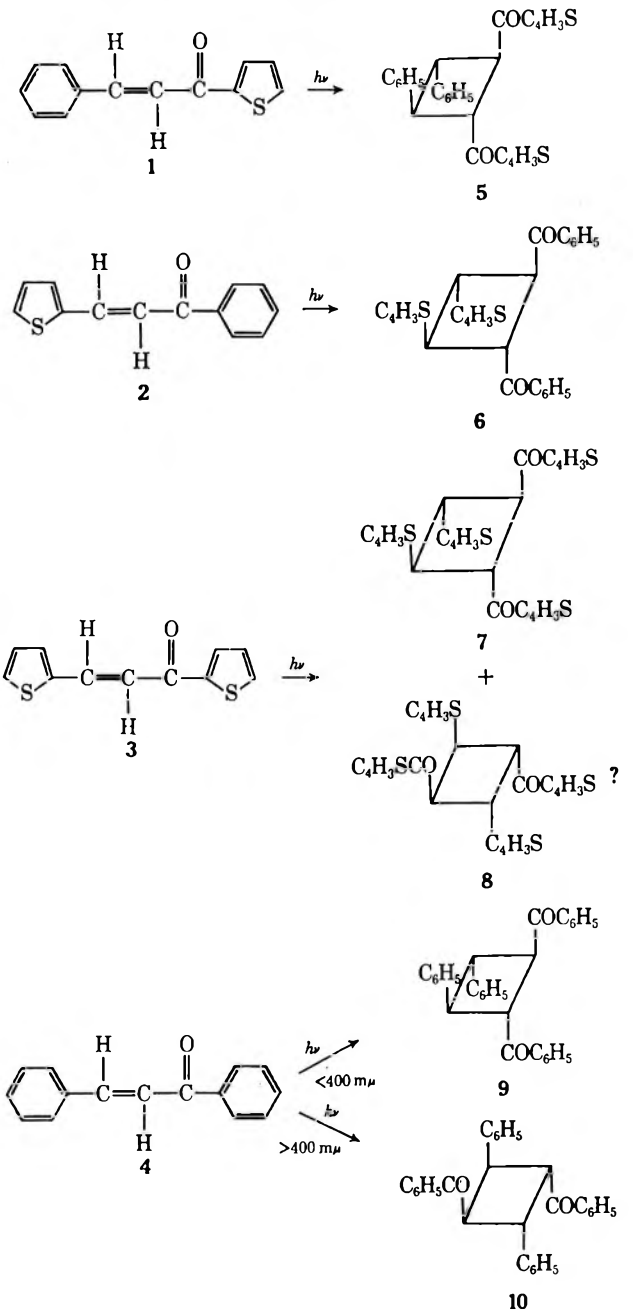
(4) R. M. Kellogg, M. B. Groen, and H. Wynberg, *J. Org. Chem.*, **32**, 3093 (1967).

(5) G. Ciamician and P. Silber, *Ber.*, **35**, 4128 (1902).

(6) Another route to cyclobutanes with thienyl substituents is the solid-state irradiation of β-(2-thienyl)acrylic acid: M. Lahav and G. M. J. Schmidt, *J. Chem. Soc. B*, 239 (1967).

(7) C. Weijgand and F. Strobelt, *Ber.*, **68**, 1839 (1935).

SCHEME I



One of the main fragments of **5** is the stilbene positive ion (*m/e* 192). We were not able to get a mass spectrum of the product formed from **3**, since it decomposed in the inlet system to the monomer **3**. Nmr data are summarized in Table I.

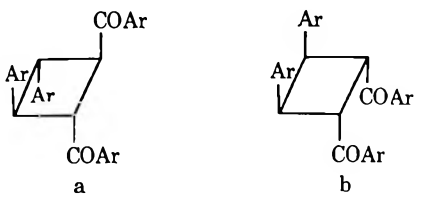
TABLE I

NMR SPECTRA OF THE DIMERS

Compd	Chemical shifts of cyclobutane protons[a] Multiplet A	Mulitplet B	Singlet
5	5.60	5.94	
6	5.47	5.82	
7	5.62	5.82	
8			5.31
9	5.38	5.97	
10			5.06

[a] All spectral are recorded in $CDCl_3$, solution with TMS as an internal standard. Chemical shifts are given in parts per million on the τ scale.

The nmr spectra of **5** and **6** showed two symmetrically arranged multiplets, characteristic for an AA'BB' system, which requires either a plane or a twofold axis of symmetry in the molecule. The products formed from **3** had an additional small broad singlet, the integration ratio multiplets:singlet being about 10:1. The nmr and mass spectral data leave for the major products two equally possible structures as depicted in A and B below. Two other structures, namely with both aroyl



groups *cis* to the adjacent aryl groups, although in principle possible, are very unlikely.

The photodimer **9** formed from chalcone has been shown by independent synthesis[8] to have the C_2 symmetric head-to-head structure A. Its nmr spectrum showed exactly the same pattern as the compounds **5**, **6**, and **7**. Moreover, the low field parts of the multiplets of **9** and **6**, caused by the protons adjacent to the aroyl groups, have almost equal chemical shifts. The same is true for the high-field parts of **9** and **5** caused by the protons adjacent to the aryl groups. These facts suggest strongly that **5**, **6**, and **7** have the same stereochemical configuration as the chalcone dimer **9**, although strictly spoken the structure B cannot be ruled out completely. The structure of the minor product, **8**, is not at all certain. We propose, however, a structure similar to that of the second chalcone dimer **10**, which is consistent with our findings that both **8** and **10** show singlets for the cyclobutane protons in the nmr spectrum. We believe that the addition of iodine to the reaction mixture causes a suppression of the *trans* to *cis* isomerization. This, in turn, inhibits polymerization of the *cis* form of the starting material.

Although the reactions described in this paper can be expected to proceed *via* triplets, we have not done experiments to prove or disprove this. The dependence of the product formation in the case of chalcone itself on the reaction conditions and especially on the wavelength suggests that the actual mechanism is quite complex.

Experimental Section

The irradiation experiments were carried out in a Rayonet reactor equipped with 350 mμ ("dark light") lamps. Nmr spectra were taken with a Varian A-60 instrument using tetramethylsilane (TMS) as an internal standard. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Mass spectra were taken with an AEI MS-902 instrument.

trans,trans,trans-**1,2-Diphenyl-3,4-di-2-thenoylcyclobutane (5). A.**—A solution of 7 g of **1** in 20 ml of chloroform was irradiated for 20 hr in ordinary micro test tubes. The solvent was evaporated and the residue was treated with hot ethanol. The ethanol solution was decanted leaving a resinous residue. This procedure was repeated twice. On standing for several days, a colorless precipitate was formed which was recrystallized from ethanol. The yield of **5** was 0.7 g (10%), mp 128–129.5°. The mass spectrum showed peaks at *m/e* 428, 410, 317, 214, and 180.

Anal. Calcd for $C_{26}H_{20}O_2S_2$: C, 72.87; H, 4.71; S, 14.96; mol wt, 428.6. Found: C, 72.74, 72.89; H, 4.73, 4.50; S, 14.90, 15.22; mol wt (osm), 425.0, 427.9.

(8) P. Adler, Thesis, Rostock, 1938; *Chem. Zentralbl.*, I, 363 (1941).

B.—To a solution of 18 g of **1** in 60 ml of chloroform, a crystal of iodine (0.2 g) was added and the solution was irradiated for 48 hr. Work-up as described above gave 4.0 g (22%) of product, mp 127–128.5°.

trans,trans,trans-**1,2-Dibenzoyl-3,4-di-2-thenoylcyclobutane (6).**—A solution of 8 g of **2** in 20 ml of chloroform was irradiated for 20 hr. The same procedure as in the previous experiments furnished 0.45 g (6%) of the product **6**, mp 132–134° (from ethanol). In a second run the irradiation time was prolonged to 48 hr. The product was obtained in 10% yield, mp 130–132°. The mass spectrum showed peaks at *m/e* 428, 410, 323, 214, and 192.

Anal. Calcd for $C_{26}H_{20}O_2S_2$: C, 72.87; H, 4.71; S, 14.96; mol wt, 428.6. Found: C, 72.80, 72.90; H, 4.82, 4.79; S, 14.82, 14.95; mol wt (osm), 416.9, 424.1.

trans,tarns,trans-**1,2-Di-2-thienyl-3,4-di-2-thenoylcyclobutane (7) and** *trans,cis,trans*-**1,3-Di-2-thienyl-2,4-di-2-thenoylcyclobutane (8).**—A solution of 8 g of **3** in 25 ml of chloroform upon irradiation for 20 hr furnished 0.3 g (4%) of a mixture of **7** and **8**, mp 124–134°. No attempts were made to separate the mixture. The mass spectrum showed only peaks with *m/e* of 220.

Anal. Calcd for $C_{22}H_{16}O_2S_4$: C, 59.97; H, 3.67; S, 29.11; mol wt, 440.6. Found: C, 60.14, 59.99; H, 3.57, 3.70; S, 29.04, 28.90; mol wt (osm), 437.4, 431.7.

trans,trans,trans-**1,2-Dibenzoyl-3,4-diphenylcyclobutane (9).**—A solution of 17 g of **4** in 50 ml of chloroform was irradiated in small quartz tubes for 20 hr. Work-up in the usual way afforded 1.0 g (6%) of product, mp 125–126.5° (lit.[2] 124–125°). By prolonging the irradiation time and adding a crystal of iodine, the yield of **9** could be improved to 28%.

trans,cis,trans-**1,3-Dibenzoyl-2,4-diphenylcyclobutane (10).**—A solution of 7 g of **4** in 20 ml of chloroform was irradiated in ordinary micro test tubes for 20 hr. After evaporation of the solvent, a yellow oil was obtained consisting mainly of starting material (*cis–trans* mixture). Ethanol was added and, on standing, starting material crystallized. It was removed by filtration. From the mother liquor 10 mg (0.15%) of **10** crystallized eventually, mp 234–236° (lit.[2] 225–226°).

Registry No.—**5**, 24825-03-4; **6**, 24825-04-5; **7**, 24825-05-6; **8**, 24825-06-7; **9**, 24825-07-8; **10**, 24825-08-9.

1,5-Hydrogen Migrations in Bicyclic Carboxaldehydes

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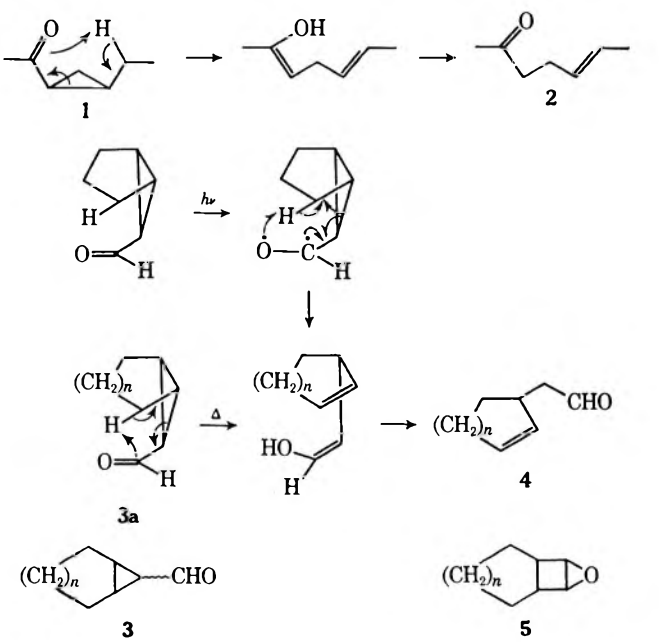
Received January 23, 1970

Cyclopropyl ketones have been reported to undergo thermal and photochemical rearrangements to homoallylic ketones (**1** → **2**).[1,2] We have observed that analogous reactions occur in bicyclic carboxaldehydes, **3** (n = 1, 2), where 1,5-hydrogen migration is possible, leading to δ^2-cycloalkenyl acetaldehydes, **4** (n = 1, 2).

Injection of the *endo* isomers of **3** (n = 1, 2) into a vapor phase chromatograph (vpc) at 190° with the injection port heated to 230° produces a single volatile compound identified as the corresponding cycloalkenyl acetaldehyde, **4** (n = 1, 2).[3] The *exo* isomers are inert under these conditions.

The dropwise addition of the *endo* isomer of **3** (n = 1) onto a column of glass beads at 300° under helium gas flow gives a crude pyrolysate whose nmr spectrum is identical with that of **4** (n = 1). The *exo* isomer of **3** (n = 1) remains unchanged at temperatures as high as 400° suggesting that the reaction is not proceeding in a stepwise fashion involving the initial cleavage of the cyclopropyl bond. The necessity for the proximity of the carbonyl group and a γ hydrogen has been demonstrated in a similar bicyclic system where initial thermal rearrangement to a cycloalkenyl acetaldehyde is postulated.[4] The thermal instability of *endo*-**3** (n = 1, 2) may account for its absence and the presence of **4** (n = 1, 2) among the products of the thermal rearrangement of the cyclobutene epoxides, **5** (n = 1, 2).[3]

The irradiation of a 1% ethereal solution of **3a** (n = 1) with 3000 Å light gives **4** (n = 1) in *ca.* 30% yield. Similar irradiation of *exo*-**3** (n = 1) gives a complex mixture of products which does not contain significant amounts of **4** (n = 1). Initial rupture of the cyclopropyl bond would give a common intermediate. An intramolecular γ hydrogen abstraction (Norrish "type II"), leading to the formation of **4**, can only occur in the *endo* isomer. It appears that this pathway is favored when possible.[2]



Experimental Section[5]

Bicyclic Carboxaldehydes (III).—The *endo* isomers of **3** (n = 1, 2) were synthesized by known procedures.[6,7] The *exo* isomers of **3** (n = 1, 2) were synthesized by epimerization of the *endo* isomers.[7] The aldehydic protons of the *exo* and *endo* isomers have different chemical shifts in their nmr spectra providing a

(1) R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *J. Amer. Chem. Soc.*, **89**, 1404 (1967). This article contains an excellent discussion of and leading references to the thermal rearrangement of cyclopropyl ketones, carboxaldehydes, and carboxylate esters.

(2) W. G. Dauben, L. Schutte, and R. E. Wolf, *J. Org. Chem.*, **34**, 1849 (1969).

(3) D. L. Garin, *ibid.*, **34**, 2355 (1969).

(4) F. Bickelhaupt, W. L. DeGraaf, and G. W. Klumpp, *Chem. Commun.*, 53 (1968).

(5) A Perkin-Elmer R-20 spectrometer was used for nmr measurements in $CDCl_3$ using TMS as internal standard. Wilkens A-700 (Autoprep) instruments were used for vpc analyses and separations utilizing silicone gum rubber (SE-30) and fluorosilicone (QF-1) as stationary phase materials.

(6) R. T. LaLonde and M. A. Tobias, *J. Amer. Chem. Soc.*, **86**, 4068 (1964); D. L. Garin, Ph.D. Thesis, Iowa State University, Ames, Iowa, 1964.

(7) D. L. Garin, Abstracts, 149th National Meeting of the American Chemical Society, Houston, Texas, 1970, Orgn 137 (submitted for publication).

rapid determination of purity. The aldehydes were readily oxidized to the known carboxylic acids for conclusive identification *via* mixture melting point determinations.[8]

Vpc Results.—The injection of up to 50 μl of **3** (n = 1, 2) into the vpc at 190° with an injection port temperature of 230° resulted in apparently quantitative rearrangment of the *endo* isomers to **4** (n = 1, 2) without affecting the *exo* isomers.[9] Typical retention times (min) for a 20 ft × $^3/_8$ in. 30% QF-1 column under a helium gas flow rate of 100 cc/min were: *exo*-**3** (n = 1), 18; **4** (n = 1), 12; *exo*-**3** (n = 2), 28; **4** (n = 2), 17. Samples were collected from the vpc and subjected to spectral analysis. The *exo* isomers were shown to be unchanged while the nmr and infrared spectra ($CHCl_3$) of **4** (n = 1, 2) were identical with that of authentic material.[3]

Pyrolysis Results.—The dropwise addition of the *endo* isomer of **3** (n = 1) onto a 9 in. column of glass beads in a temperature controlled oven at 240° under helium gas flow and flushing with ether gives a crude pyrolysate containing 25% of **4** (n = 1) and 75% of starting material determined by integration of the aldehydic protons at δ 9.85 (t) and 9.55 (d), respectively. At 300°, the nmr spectrum of the crude pyrolysate is identical with that of **4** (n = 1). The *exo* isomer of **3** (n = 1) remains unchanged at temperatures as high as 400° determined by nmr analysis of the crude pryolysate.

Photochemical Rearrangements.—A solution of 60 mg of *endo*-**3** (n = 1) in 7 ml of ether was irradiated with 3000 Å light in a quartz tube in a Rayonet reactor for 5 hr. Some polymeric material had formed on the sides of the tube. The ether was removed *in vacuo* and $CDCl_3$ added to the residue (54 mg). Comparison of the nmr spectrum of this material with that of **4** (n = 1) allowed an estimation of *ca.* 30% of **4** (n = 1) in the crude mixture from integration of the aldehydic and olefinic protons against the total proton count in the nmr spectrum of the crude reaction mixture. Similar irradiation of 65 mg of *exo*-**3** (n = 1) in 7 ml of ether gave a product mixture whose nmr spectrum showed that more than 90% of the starting material had reacted but there were no olefinic absorptions.

Registry No.—*endo*-**3** (n = 1), 4729-42-4; *endo*-**3** (n = 2), 24874-09-7.

Acknowledgment.—The support of the Petroleum Research Fund (1207-G1) and the Research Committee-UMSL is gratefully acknowledged.

(8) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Amer. Chem. Soc.*, **85**, 582 (1963); J. A. Berson and E. S. Hand, *ibid.*, **86**, 1978 (1964). The author is indebted to Professor Berson for an authentic sample of bicyclo-[4.1.0]heptan-7-*endo*-carboxylic acid.

(9) No other peaks are observed in the chromatogram but preparative collection from the vpc results in 80–90% recovery. This loss, due to incomplete trapping of the effluent, is not unusual.

Chloromethyl Sulfoxides and Sulfones from 1,2-Dichlorovinyl Sulfoxides and Sulfones

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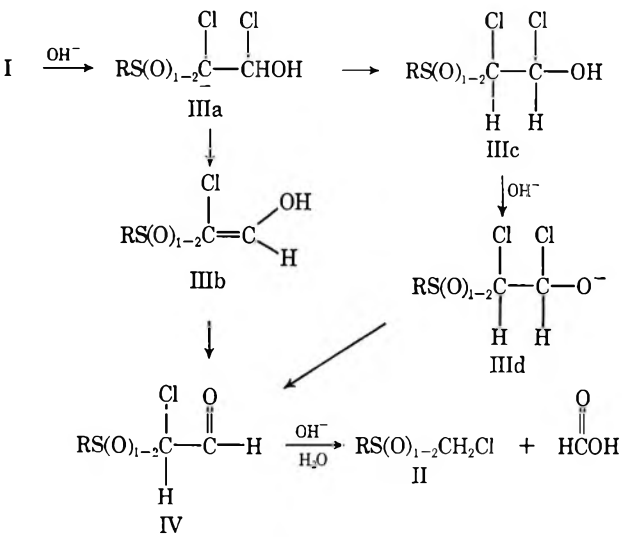
Received January 28, 1970

There has been considerable recent interest in the preparation and chemistry of α-chloro sulfoxides[1] and in the chemistry of sulfoxides in general.[2] We report here the facile preparation of α-chloro sulfoxides and sulfones from the corresponding 1,2-dichlorovinyl compounds by treatment with dilute aqueous base. In Table I are listed a number of examples of this reaction and the recrystallized yields of the products.[3-6] Crude yields were generally 10 to 15% higher, and the crude products were quite clean, impurities being soluble in the basic aqueous phase. Identification of products was made by elemental analyses and spectral (ir and nmr) and melting point comparison with authentic samples prepared by oxidation of the corresponding α-chloro sulfides.[7,8]

In only one case, that of the *t*-butyl sulfoxide IIc, was a relatively poor yield obtained. Part of the starting material was converted into unidentified base-soluble products under all conditions explored. The use of organic solvents such as dioxane, tetrahydrofuran, dimethyl sulfoxide, and dimethylformamide in conjunction with the aqueous base for the hydrolysis of Ia–c led uniformly to lower yields of IIa–c. Milder conditions were necessary with the benzyl derivatives Ie–f, as heating led to styrene from the chloromethyl sulfone IIf *via* a Ramberg–Backlund reaction and to unidentified products from the sulfoxide IIe.



The chemistry of β-chlorovinyl sulfones has been extensively investigated and reaction with various nucleophiles (RO^-, RS^-, RSO_2^-, R_2NH) leads to β-substituted vinyl sulfones with displacement of chloride.[4,9] Thus, it is reasonable to postulate that the initial step in the present reaction is nucleophilic attack by hydroxide to give the carbanion IIIa, which can be converted to the aldehyde IV either by direct elimination of chloride to give the tautomeric enol IIIb, or by protonation to give IIIc followed by elimination of HCl through IIId. The aldehyde would be highly susceptible to attack by hydroxide followed by cleavage to give formic acid and the α-sulfinyl or sulfonyl anion which

(1) (a) R. N. Leoppky and D. C. K. Chang, *Tetrahedron Lett.*, 5415 (1963); (b) M. Hojo and Z. Yoshida *J. Amer. Chem. Soc.*, **90**, 4496 (1968); (c) T. Durst, *ibid.*, **91**, 1034 (1969).

(2) C. R. Johnson and J. R. Sharp, "The Chemistry of Sulfoxides," Intra Science Research Foundation, Santa Monica, Calif., 1969.

(3) E. Ayca, *Fac. Sci. Univ. Istanbul, Ser. C*, **22**, 371 (1957); *Chem. Abstr.*, **53**, 11287*f* (1959).

(4) H. J. Backer, *et al.*, *Rec. Trav. Chim. Pays-Bas*, **72**, 813 (1953); *Chem. Abstr.*, **49**, 11538*g* (1955).

(5) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **73**, 5187 (1964).

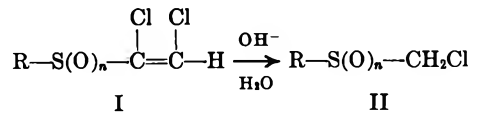
(6) J. Metivier, U. S. Patent 2,793,234 (1957).

(7) H. Bohme, *Ber.*, **69**, 1610 (1936).

(8) In agreement with Durst,[1c] we find that *m*-chloroperbenzoic acid oxidation, using chloroform or methylene chloride as solvent, gives excellent yields of the sulfoxides.

(9) F. Montanari and A. Negrini, *Gazz. Chim. Ital.*, **87**, 1068 (1957); *Chem. Abstr.*, **52**, 9987*g* (1958). L. Maioli and G. Modena, *ibid.*, **89**, 854 (1959); *Chem. Abstr.*, **54**, 22451*i* (1960).

TABLE I

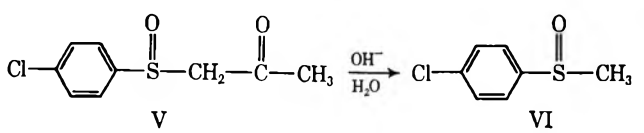


I II

Compd	R	n	Reaction conditions	Mp, °C	% yield	References: Product	References: Starting material
IIa	p-$CH_3C_6H_4$–	1	3 hr, reflux	60–62	81	3	6
IIb	p-$CH_3C_6H_4$–	2	4 hr, reflux	80–82	79	3	6
IIc	$(CH_3)_3C$–	1	0.5 hr, reflux	73–75	48		4
IId	$(CH_3)_3C$–	2	4 hr, reflux	83–85	81	4	4
IIe	$C_6H_5CH_2$–	1	44 hr, ambient	64–67	78		6
IIf	$C_6H_5CH_2$–	2	48 hr, ambient	97–99	77	5	6

would be rapidly protonated to give the base-stable final product II. Such cleavages of β-keto sulfones are well documented.[10]

The aldehydes IV have not been observed by us, even in basic and acidic extracts of reactions terminated when greater than 50% of starting material I remains. However, Backer[4] reported the preparation of the *t*-butylsulfonylaldehyde IVd by acid cleavage of the corresponding dimethyl acetal and its ready basic hydrolysis to the chloromethyl sulfone IId. There appears to be no report of the basic cleavage of β-keto sulfoxides, although the reaction is essentially the reverse of the synthetic method developed by Corey[11] and Russell[12] for their preparation from a sulfinyl carbanion and an ester. We found that the β-keto sulfoxide V was cleaved in 93% yield to the known methyl sulfoxide VI[13] by refluxing with 5% sodium hydroxide for 18 hr.



V VI

Experimental Section

Hydrolysis of Dichlorovinyl Sulfoxides and Sulfones.—The appropriate starting material,[4,6] 5 g, was added to 100 ml of 5% aqueous sodium hydroxide plus a small amount of a surfactant (Aerosol OTB). The mixture was stirred under the conditions given in Table I. The products were isolated by extraction with chloroform and purified by recrystallization from a benzene–hexane mixture. Direct comparison of physical properties was made in each case with authentic samples prepared according to the literature or as indicated below to substantiate the structure of the products.

Preparation of Sulfoxides IIc, IIe, and V.—To a solution of the corresponding sulfide (0.1 mol) in 250 ml of chloroform cooled in an ice bath was added as a solid over 1 hr *m*-chloroperbenzoic acid (0.1 mol). The solution was left at room temperature for 24 hr, filtered to remove precipitated *m*-chlorobenzoic acid, washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated, and the product recrystallized from benzene–hexane to give the following in yields above 80%.

IIc: mp 73–75°; nmr ($CDCl_3$) δ 1.33 (s, 9, $(CH_3)_3C$·), 4.35 (q, 2, CH_2Cl). *Anal.* Calcd for $C_5H_{11}ClOS$: S, 20.71; Cl, 22.95. Found: S, 20.60; Cl, 23.05.

IIe: mp 64–67°; nmr ($CDCl_3$) δ 4.36 (m, 4, $-CH_2S(O)CH_2Cl$), 7.36 (s, 5, C_6H_5). *Anal.* Calcd for C_8H_9ClOS: S, 16.95; Cl, 18.82. Found: S, 16.72; Cl, 18.68.

V: mp 109–111°; nmr ($CDCl_3$) δ 2.25 (s, 3, $C(O)CH_3$), 3.90 (s, 2, $S(O)CH_2$), 7.53 (m, 4, $Cl-C_6H_4(O)S-$). *Anal.* Calcd for $C_9H_9ClO_2S$: S, 14.75; Cl, 16.35. Found: S, 14.40; Cl, 16.56.

Registry No.—IIa, 24824-93-9; IIb, 7569-26-8; IIc, 24824-95-1; IId, 24824-96-2; IIe, 24824-97-3; IIf, 5335-44-4; V, 17530-95-9.

(10) (a) A. Otto, *J. Prakt. Chem.*, **36**, 401 (1888). (b) M. Ohta, *et al.*, *J. Pharm. Soc. Jap.*, **69**, 43 (1949); *Chem. Abstr.*, **44**, 1485*c* (1950). (c) J. J. Looker, *J. Org. Chem.*, **31**, 2714 (1966).

(11) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964).

(12) H. D. Becker, G. J. Mikol, and G. A. Russell, *ibid.*, **85**, 3410 (1963).

(13) A. Cerniani and G. Modena, *Gazz. Chim. Ital.*, **89**, 843 (1959); *Chem. Abstr.*, **54**, 22446*i* (1960).

Conjugated Epoxy Compounds. An Unusual Ring Contraction of *trans*-2,3,5,6-Diepoxy-2,5-di-*t*-butyl-1,4-benzoquinone upon Reaction with Diazomethane

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Compounds containing functional groups having partial sp^2 character which are specifically oriented in close proximity around a small carbon framework are of potential interest in regard to unusual spectral and chemical properties. Reported here is an investigation leading to such a system, *i.e.*, the tri- and tetraepoxides, **2** and **3**, respectively. These compounds are obtained from the reaction of *trans*-2,3,5,6-diepoxy-2,5-di-*t*-butyl-1,4-benzoquinone (**1**)[1-3] with either diazomethane or sulfonium methylides. Reaction of **1** with the former reagent also results, in addition to epoxidation, in an unusual ring contraction to the ketone (**4**). This result, to our knowledge, constitutes the first such rearrangement involving diazomethane and suggests an interesting area for subsequent investigations utilizing simpler epoxy ketones.

Reaction of an ethanolic solution of **1** with excess freshly distilled ethereal diazomethane[4] resulted in the evolution of nitrogen; formation of the organic products was conveniently monitored by glc,[5] showing the gradual formation of the triepoxide **2** which subsequently disappeared with the synchronous formation of

(1) H. W. Moore, *J. Org. Chem.*, **32**, 1996 (1967).

(2) F. R. Hewgill and S. L. Lee, *J. Chem. Soc. C*, 1549 (1968).

(3) D. H. Williams, J. Ronayne, H. W. Moore, and H. R. Sheldon, *J. Org. Chem.*, **33**, 998 (1968).

(4) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

(5) Analysis was carried out isothermally at 190° on 6 ft × 1/4 in. SE-30/Chromosorb W columns. Thermal conductivity and flame ionization were used as the methods of detection.

the tetraepoxide **3** and the ring contracted ketone **4**. Termination of the reaction at the appropriate time gave the triepoxide (**2**) in 61% yield, while after complete reaction the only products were **3** and **4** in a ratio of 8:2, respectively. That the triepoxide **2** is a precursor to compounds **3** and **4** was shown by subjecting it to the reaction conditions and observing the formation of the products, **3** and **4**, in the same (8:2) relative ratio.

Critical structural data for compounds **2**, **3**, and **4** follow. Compound **2**: mp 111–114°; ir (Nujol) 1693 (C=O), 900–950 cm^{-1} (C—C); nmr (CCl_4) δ 0.99 [s, 9, $C(CH_3)_3$], 1.05 [s, 9, $C(CH_3)_3$], 2.63 [s, 1, CH], 3.30 (s, 1 CH), 3.14 (AB, 2, J = 4.5 cps, CH_2); mass spectrum M^+ 266. Compound **3**: mp 114–115°; ir (Nujol) 900–960 cm^{-1} (C—C); nmr (CCl_4) δ 1.00 [s, 18, $C(CH_3)_3$], 2.75 (AB, 4, J = 6.8 cps, CH_2), 3.36 [s, 2, CH]; mass spectrum M^+ 280. Compound **4**, mp 105–107°; ir (Nujol) 1739 (C=O), 947, 900 cm^{-1} (C—C); nmr (C_6H_6) (220 Mc)[6] δ 0.92 [s, 9, $C(CH_3)_3$], 0.99 [s, 9, $C(CH_3)_3$], 2.82 (AB, 2, J = 5 cps, CH_2), 3.52 (s, 1, CH), 3.86 (AB, 2, J = 17 cps, CH_2), 4.61 (s, 1, CH) (in carbon tetrachloride these peaks appear, respectively, at δ 0.97 1.12, 3.00, 3.51, 3.78, and 4.42); mass spectrum M^+ 280. The mass spectrum of **4** is relatively simple showing only three peaks with relative abundance greater than 15% in the mass range above m/e 57. These peaks appear at m/e 180 (23%), 222 (41%), and 207 (100%) and are rationalized in accordance with structure **4** as shown in Scheme I. A sample of **4** in which the methylene group α to the carbonyl was deuterated was obtained from the reaction of the triepoxide **2** with deuterated diazomethane. The mass spectrum showed the same three major peaks as those reported above for the proteated isomer. The only major difference is the molecular ion peak at m/e 282 and the M − 15 peak at m/e 267.

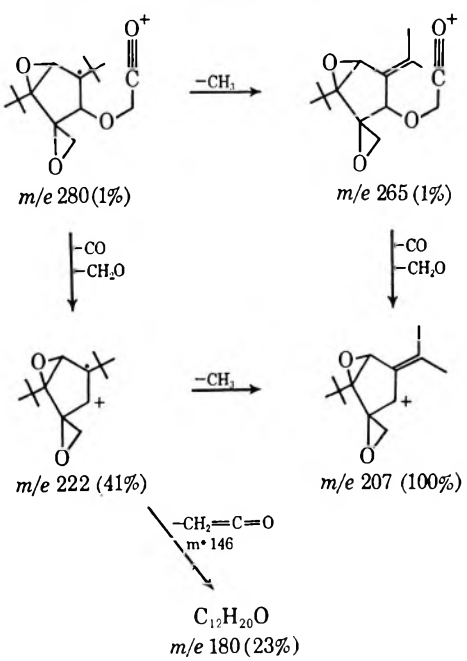
The yield of the ring contracted ketone **4** ranges from 1.2 to 32.2% depending upon the solvent. The following relative ratios of **3** to **4** are illustrative of this solvent dependence: ether 99:1, ethanolic ether 8:2, aqueous methanolic ether 7:3, lithium bromide methanol (1:1 lithium bromide to substrate) 6.2:3.8.[7]

The stereochemistry of the new compounds reported here are not proved in an unambiguous way. It is assumed, and substantiated partially by experiments, that attack of diazomethane proceeds from the least hindered side of the molecule, *i.e.*, the side opposite the *t*-butyl groups.[8] Since the triepoxide **2** is a precursor to the tetraepoxide **3**, and the nmr spectrum of **3** shows the molecule to be completely symmetrical, the stereochemistries as represented by formulas **2** and **3** are most reasonable.

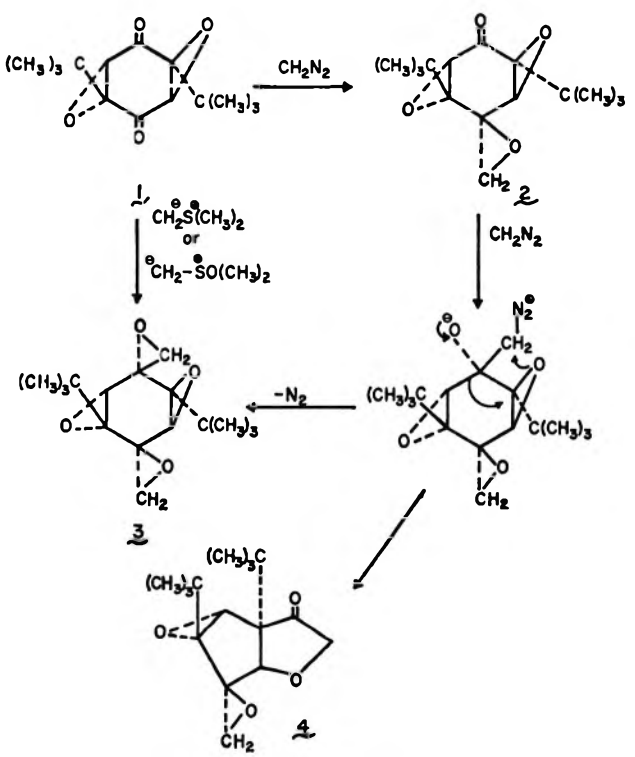
Consistent with the above steric control argument is the fact that the reaction of **1** with either dimethyloxosulfonium methylide or dimethylsulfonium methylide also give exclusively compounds **2** and **3**. However, it is interesting to note that these ylide reactions give no trace of the ring contracted ketone **4**.

The stereochemistry of **4** is predicted on the basis of the mechanism presented in Scheme II, assuming a con-

Scheme I



Scheme II



(6) The authors are grateful to the California Institute of Technology for the 220 Mc nmr spectrum and to the National Science Foundation for making this instrument available for regional use.

(7) These results are in agreement with previous observations concerning the influence of acidic solvents on epoxidation and homologation, *i.e.*, as the acidity of the reaction medium increases, epoxidation is retarded and homologation is enhanced. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967.

(8) Drieding models show that the diepoxide **1** can exist in two degenerate conformations, and that one of the carbonyl groups is always less sterically hindered on the side opposite the bulky alkyl group, the other carbonyl being coplanar with the alkyl substituent.

certed ring contraction. Note that the epoxide oxygen which is involved in this ring contraction reaction is the one on the same side as the methylene of the diazomethane adduct, thus leading to the *cis* ring junction in **4**. One would predict on the basis of a concerted ring contraction that rearrangement would be much less favorable, if possible at all, for those epoxy ketones in which the diazomethane attacks from the side opposite the epoxide function. Such systems are currently under investigation and the results along with those obtained concerning the conjugative influences of the epoxide functions on the spectral and chemical properties of compounds such as **1**, **2**, and **3** will be reported in a subsequent communication.

Experimental Section

Reaction of *trans*-2,3,5,6-diepoxy-2,5-di-*t*-butyl-1,4-benzoquinone (1) with Ethereal Diazomethane.—Excess freshly distilled ethereal diazomethane was added to a solution of 0.318 g (0.00126 mol) of the diepoxide **1** in 50 ml of anhydrous diethyl ether. Nitrogen slowly evolved and the reaction course was followed by glc which showed the progressive appearance of the triepoxide **2** followed by its disappearance and the formation of the tetraepoxide **3** and the ketone **4**. After 24 hr the solvent was removed *in vacuo* leaving 0.339 g of a white crystalline product. Glc analysis of this solid showed it to be a mixture of the tetraepoxide **3** and the ketone **4** in a ratio of 98.8:1.2, respectively. Recrystallization of this solid from ethanol gave the pure tetrapoxide **3**, mp 114–115°.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.52; H, 8.65.

The ring contracted ketone **4** was isolated and purified by preparative glc, mp 105–107°.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.43; H, 8.49.

Reaction of the diepoxide **1** with ethereal diazomethane in solvents of varying acidity changed the ratio of the products **3** and **4**.

To a solution of 0.278 g (0.0011 mol) of the diepoxide **1** in 100 ml of absolute ethanol was added excess ethereal diazomethane. Concentration of the reaction solution after nitrogen evolution ceased gave 0.292 g (0.0010 mol) of a white crystalline solid. Gas chromatographic analysis of this product showed it to be a mixture of **3** and **4** in a ratio of 79.9 to 20.1, respectively.

Reaction of 0.439 g (0.0017 mol) of **1** in 10 ml of water and 100 ml of absolute methanol with excess etheral diazomethane gave 0.464 g (0.0017 mol) of a white solid. This solid was shown by gas chromatographic analysis to be a mixture of **3** and **4** in a ratio of 71.7 to 28.3, respectively.

Reaction of 0.387 g (0.0015 mol) of **1** in a solution of 100 ml of absolute methanol and 0.133 g (0.0015 mol) of lithium bromide with excess ethereal diazomethane gave 0.407 g (0.0015 mol) of a white crystalline solid. This solid was isolated by concentration of the reaction mixture followed by repeated washing of the precipitate with water to remove all traces of lithium bromide. Gas chromatographic analysis of this product showed it to be a mixture of **3** and **4** in a relative ratio of 61.8 to 38.2, respectively.

Tripoxide 2.—Reaction of the diepoxide **1** with diazomethane was carried out according to the method described above. The reaction was worked up when the triepoxide **2** was at its maximum concentration (61%) as evidenced by glc (approximately 6 hr). Recrystallization several times from ethanol gave the pure triepoxide **2**, mp 111–114°.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.68; H, 8.27. Found: C, 67.65; H, 8.33.

Reaction of the Triepoxide 2 with Deuterated Diazomethane.—Deuterated diazomethane was prepared in a solvent system of tetrahydrofuran, D_2O, and phenol-O-*d*.[9] One hundred milligrams of the triepoxide **2** was added to this solution and was allowed to react for 12 hr. The solvent was then removed and the product dried *in vacuo*. Gas chromatographic analysis of the product showed only the tetraepoxide **3** and the ketone **4** in approximately a ratio of 98:2, respectively. The products were separated by preparative glc. The nmr spectrum of the tetraepoxide showed at least 96% deuterium incorporation at one of exocyclic epoxy methylenes. The mass spectrum of the ketone **4** is described in the text.

Reaction of *trans*-2,3,5,6-Diepoxy-2,5-di-*t*-butyl-1,4-benzoquinone (1) with Dimethylsulfonium Methylide.—To a cold, freshly prepared DMSO solution of dimethylsulfonium methylide[10] was added 2.523 g of finely powdered diepoxide **1** as a DMSO slurry. The reaction solution was allowed to warm to room temperature and then poured into 500 ml of water. The white precipitate (1.917 g, 68.5% yield) was collected and shown to be the tetraepoxide **3** by mixture melting point, and comparison of its ir and nmr spectra to those of an authentic sample. Glc analysis of the crude product showed *only* the tetraepoxide **3**.

Reaction of *trans*-2,3,5,6-Diepoxy-2,5-di-*t*-butyl-1,4-benzoquinone with Dimethyloxosulfonium Methylide.—The reaction of the diepoxide **1** with dimethyloxosulfonium methylide[10] was carried out in a manner analogous to that described above with dimethylsulfonium methylide. The product was again shown to be only the tetraepoxide **3** by glc, mixture melting point, and its ir and nmr spectra.

Registry No.—**1**, 10476-78-5; **2**, 24903-91-1; **3**, 24903-92-2; **4**, 24903-93-3; diazomethane, 334-88-3.

Acknowledgment.—The authors are grateful to the National Science Foundation for partial financial support (GP 8706) of this work. We also express appreciation to Dr. Jean-Claude Gramain for helpful discussions.

(9) D. W. Thomas and K. Biemann, *J. Amer. Chem. Soc.*, **87**, 5447 (1965).

(10) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1357, 1355 (1965).

Applications of Rare Earth Nuclear Magnetic Resonance Shift Reagents. II.[1] The Assignment of the Methyl Proton Magnetic Resonances of *d*-Camphor

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When the dipyridine adducts of trisdipivalomethanato rare earth chelates,[2] $M(DPM)_3 \cdot 2py$, are dissolved in carbon tetrachloride, the molecules dissociate according to equations of the type

$$M(DPM)_3 \cdot 2py \rightleftharpoons M(DPM)_3 \cdot py + py \quad (1)$$

$$M(DPM)_3 \cdot py \rightleftharpoons M(DPM)_3 + py \quad (2)$$

If an organic compound, B, having a basic coordinating group is added to the above solution, associations with the metal complexes may occur of the type

$$M(DPM)_3 \cdot py + B \rightleftharpoons M(DPM)_3 \cdot pyB \quad (3)$$

Contact shifts in the pmr spectrum of B are a consequence of this association if M is paramagnetic. The phenomenon of contact shifts has been known and studied for many years, as has the requirement for the observation of narrow nmr absorptions in paramagnetic systems, eq 4, where T_e is the electronic relaxation

$$\frac{1}{T_e} > a \quad (4)$$

(1) Part I: C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969).

(2) Dipivalomethane, HDPM, is 2,2,6,6-tetramethylheptane-3,5-dione.

time and a is the coupling constant between the electronic and nuclear moments.[3] Frequently the condition for narrow nmr absorptions (eq 4) is not met. This is commonly the case for complexes of short transition series metals, many of which have electronic relaxation times long enough for epr spectra to be observed in liquid solutions. In contrast, paramagnetic rare earth complexes (with the exception of gadolinium) are characterized by relatively short electron relaxation times[4] and solvent nmr resonances of rare earth complex solutions are typically not seriously broadened. Four paramagnetic members (Pr, Nd, Sm, Eu) of the series of rare earth compounds $M(DPM)_3 \cdot 2py$ exhibit pmr spectra in solution which indicates that the condition of eq 4 is met for those compounds. Additionally, the pmr spectrum of the europium member of the series is silent in the spectral region in which the pmr absorptions of most organic compounds are found. Therefore, $Eu(DPM)_3 \cdot 2py$ exhibits a combination of chemical (eq 3) and magnetic properties which make it well suited for use as a probe in the pmr study of a wide variety of organic compounds. Though $Eu(DPM)_3 \cdot 2py$ appears to be unique in the above series, this combination of properties should be relatively common for rare earth compounds.

Recently,[1] a study was reported of contact shifts produced in the pmr spectrum of cholesterol through association with $Eu(DPM)_3 \cdot 2py$ in carbon tetrachloride solution. Among other things it was found that substantial paramagnetic shifts could be induced in the pmr spectrum of cholesterol without serious broadening effects and that the shifts produced were predominantly the result of pseudocontact interactions[5] (equation 5).

$$\frac{\Delta H}{H_j} = -\epsilon\frac{(g_1 + g_2 + g_3)}{R_j^3}\left[\left(g_1 - \frac{1}{2}g_2 - \frac{1}{2}g_3\right)(\cos^3 X_j - 1) - \frac{1}{2}(g_2 - g_3)\sin^2 X_j \cos 2\Omega_j\right] \quad (5)$$

The study of cholesterol and studies of other compounds[6] using $Eu(DPM)_3 \cdot 2py$ further indicate that the pseudocontact shifts induced are dominated by the distance parameter, R (eq 4). Magnitudes of the observed contact shifts depend upon the relative concentration of the metal complex, which indicates a rapid chemical exchange between associated and unassociated B, and the equilibrium constant for the association (eq 3) as well as the distance, R, from the metal ion to the proton in the metal chelate–organic substrate complex. Association constants, as reflected in observed contact shift magnitudes, correlate well with the basicity of the coordinating groups. Shifts of several hundred cycles, without appreciable broadening, have been obtained in the pmr spectra of organic molecules with amine and hydroxyl functional groups through association with $Eu(DPM)_3 \cdot 2py$. Compounds having a functional groupings less basic than amines and alcohols, such as esters, carbonyls, ether linkages, sulfides, sulfoxides, and others, generally associate with the metal complex to a lesser degree. These findings suggest that the compound, $Eu(DPM)_3 \cdot 2py$, and others with similar magnetic and chemical properties would be useful in pmr spectral analysis. Specifically, the sensitive distance dependence of the pseudocontact shift should indicate relative distances of protons from coordinating groups and allow assignment of resonance lines on this basis. A typical application would include the following steps. (1) Pmr spectra of the organic compound B dissolved in carbon tetrachloride are recorded after successive dropwise additions of $Eu(DPM)_3 \cdot 2py$ solution and the field position of the nmr lines are plotted as a function of metal concentrations. A concentration study is not necessary in principle as the paramagnetic shifts measured for a single metal concentration are sufficient, but since the shifts produced may be substantial, this procedure may help keep track of the resonances and allows finer control over the shifts induced. (2) A molecular model of the compound is constructed and distances, R, from the center of the metal ion (ionic radius of Eu^{3+} = 0.950 Å) at the point of coordination to the various protons are measured. Resonances of protons closest to the coordinated metal ion will be shifted the most and assignments are made accordingly. Since the pseudocontact interaction dominates the observed shifts in aliphatic systems, many ambiguities may be resolved by plotting the measured shifts for the particular metal concentration chosen *vs.* $1/R^3$.

d-Camphor was chosen to demonstrate the above technique with the aim of confirming the methyl resonance assignments. Kumler, Shoolery, and Brutcher[7] reported initial assignments in 1958 and Tori, Hamashima, and Takamizawa[8] proposed assignments in 1964 of τ 9.02 for the C(10) methyl and 9.08 and 9.15 for the C(9) and C(8) methyls respectively in chloroform. Connolly and McCrindle[9] found apparently anomalous solvent shifts for *d*-camphor and in 1965 reassigned the resonances by deuterium substitution experiments. These corrected assignments are τ 9.02 for the C(9) methyl, 9.08 for C(10), and 9.15 for C(8) and relieve the solvent shifts of anomoly.

Pmr spectra of *d*-camphor (Figure 1) were taken with a Varian HA100 pmr spectrometer and the field positions of the methyl resonances were plotted as a function of $Eu(DPM)_3 \cdot 2py$ concentration (Figure 2). A molecular model (scale: 1 inch/Å) of *d*-camphor was constructed and approximate metal ion–methyl group distances were measured (Table I).

TABLE I
APPROXIMATE METAL–METHYL DISTANCES

Methyl group	R
C(8)	5.25
C(9)	7.0
C(10)	4.5

(3) Recent reviews include (a) M. Base, *Progr. Nucl. Magn. Resonance Spectrosc.*, **4**, 335 (1969); (b) D. R. Eaton, "Physical Methods in Advanced Inorganic Chemistry," H. A. D. Hill and P. Day, Ed., Interscience, New York, N. Y., 1968, p 462.

(4) A. Carrington and A. D. McLachlan, "Introduction to Magnetic Resonance," Harper and Row, New York, N. Y., 1967, p 173.

(5) This equation is an example taken from G. N. La Mar, W. DeW. Horrocks, and L. C. Allen, *J. Chem. Phys.*, **41**, 2126 (1964), for shifts, ΔH, produced in the resonance of the jth proton in a metal complex having a totally anisotropic g-factor. R_j is the distance from the metal to the jth proton and X_j and Ω_j are angles taken from the symmetry axes of the complex. The derivation of this equation includes assumptions appropriate to short transition series metals and is not directly applicable to rare earth complexes. However, the R parameterization is appropriate and equations for rare earth complexes are under study.

(6) C. C. Hinckley, unpublished research.

(7) W. D. Kumler, J. N. Schoolery, and F. V. Brutcher, Jr., *J. Amer. Chem. Soc.*, **80**, 2533 (1958).

(8) K. Tori, Y. Hamashima, and A. Takamizawa, *Chem. Pharm. Bull.*, **12**, 924 (1964).

(9) J. D. Connolly and R. McCrindle, *Chem. Ind. (London)*, 379 (1969).

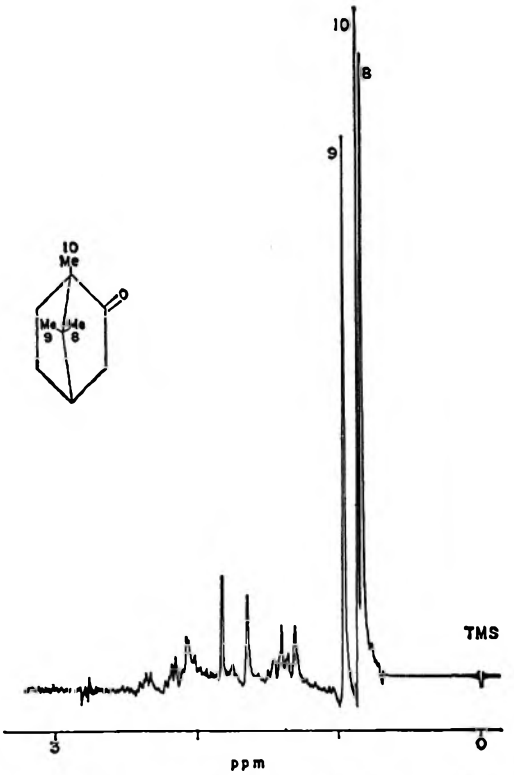

Figure 1.—Pmr spectrum of *d*-camphor. Methyl resonance assignments are indicated by number according to the accompanying diagram.

Bonding between the metal ion and the carbonyl group of *d*-camphor is expected to involve the nonbonding electron pairs of the oxygen which places the metal ion in the plane defined by the carbonyl group and the two adjacent ring carbons. Consideration of steric interference suggests that the C–O–Eu bond is bent away from the 10 methyl group. The C–O–Eu bond angle is unknown but should be between 120 and 180°. Metal ion–methyl distances to the **8** and **9** methyl groups are insensitive to the C–O–Eu angle in that portion of the plane.

Figure 2 shows that each methyl resonance is effected by the contact shift to a different degree and assignments are made accordingly (Figure 1). The 10 methyl group will be closest to the metal ion in the complex and is therefore assigned the resonance at 0.86 ppm which undergoes the greatest shift. The resonance at 0.83 ppm is shifted by an intermediate amount and is assigned to the 8 methyl. The remaining, least affected resonance, at 0.95 ppm is assigned to the 9 methyl which is furthest removed from the metal ion on coordination. These assignments are the same as those reported by Connolly and McCrindle when the solvent change from chloroform to carbon tetrachloride is taken into account.[10]

d-Camphor is a rigid structure of relatively low base strength. Comparable studies with alcohols and amines yield shifts of a greater order of magnitude. When the subject molecule, B, is flexible so that there is substantial internal rotation in the metal chelate–organic substrate complex, resonances are shifted by increments appropriate to the *average* distance from the metal in the complex. In such cases all ambiguities may not be removed. However, the use of rare earth induced contact shifts in pmr spectral analysis[11] should be applicable to studies of a wide variety of compounds and is simple enough to be routinely applied.[12]

(10) J. D. Connolly and R. McCrindle, *J. Chem. Soc. C*, 1613 (1966).

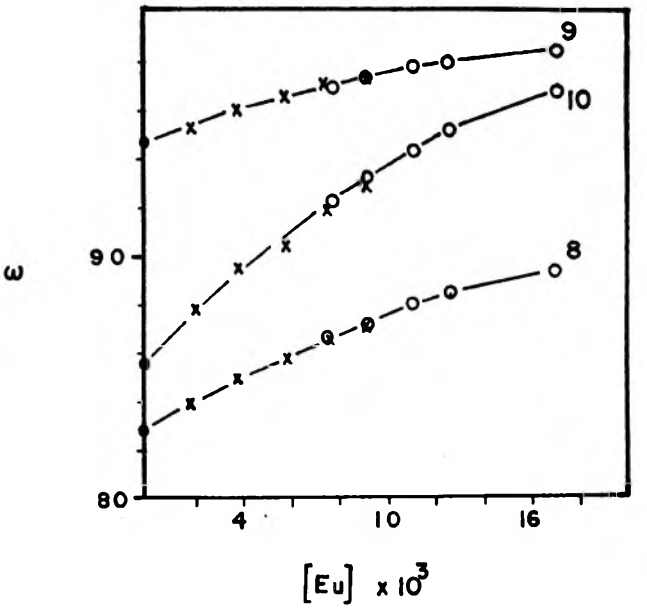

Figure 2.—Field position of the *d*-camphor methyl resonances plotted as a function of Eu(DPM)$_3$·2py concentration in cps downfield from the tetramethylsilane resonance.

Experimental Section

Preparation of Eu(DPM)$_3$·2py.—The europium chelate Eu(DPM)$_3$ was prepared by the method of Eisentrant and Sievers[14] and the dipyridine adduct obtained by recrystallization from pyridine.

Pmr Spectra.—Pmr spectra were obtained using a Varian HA100 nmr spectrometer. To 50 drops of a 0.2 *M* *d*-camphor solution in carbon tetrachloride in an nmr sample tube, 5 drops of TMS internal standard was added. Spectra were recorded and line positions measured after successive dropwise additions of 0.1 *M* Eu(DPM)$_3$·2py in carbon tetrachloride.

Registry No.—Eu(DPM)$_3$·2py, 24189-43-3; *d*-camphor, 464-49-3.

Acknowledgment.—Conversations with Dr. C. Y. Meyers of Southern Illinois University and his research group were extremely helpful. Dr. A. M. Malte graciously provided important literature references unknown to the author. The Varian HA100 nmr spectrometer was purchased with the aid of a grant from the National Science Foundation.

(11) Recent studies using Co^{2+} complexes in a similar context are: (a) C. C. McDonald and W. D. Phillips, *Biochem. Biophys. Res. Commun.*, **35**, 43 (1969); (b) W. A. Szarek, E. Dent, T. B. Grindley, and M. C. Baird, *Chem. Commun.*, **D17**, 953 (1969).

(12) Sanders and Williams[13] have shown that the chelate Eu(DPM)$_3$ produces shifts approximately four times larger than the dipyridine adduct, and have suggested additional applications. Their studies show that pyridine is not an essential component.

(13) J. K. M. Sanders and D. H. Williams, *Chem. Commun.*, **D7**, 422 (1970).

(14) K. J. Eisentrant and R. E. Sievers, *J. Amer. Chem. Soc.*, **87**, 5254 (1965).

Sulfilimines and Sulfenamides Derived from N-Chlorobenzimidates and Sulfur Nucleophiles

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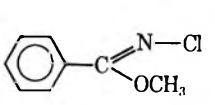
N-Haloimidates were first prepared in 1896 by Stieglitz[1] through the chlorination of ethyl benzimidate hydrochloride with cold, aqueous sodium hypochlorite solution. Subsequently, additional examples of N-chloro- and N-bromoimidates were reported[2-4] using the same general synthetic procedure. Direct halogenation of the free basic imidate esters with bromine,[5] iodine,[5] and *t*-butyl hypochloride[6] have also been described. Additionally, Stieglitz has reported[2,7] an elegant synthesis of N-haloimidates by treating N-chlcrobenzamides with diazomethane.

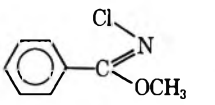
The N-haloimidates prepared were not well characterized structurally by present-day standards and their chemistry was not widely studied. The early workers devoted their efforts to a study of *syn–anti* isomerization of the N-haloimino group of these compounds.[2,3] Russian workers found that N-dialkoxyphosphinylimidates[8,9] could be prepared from the reaction of N-chlorobenzimidates with trialkyl phosphites while the use of triaryl phosphites and triaryl phosphines in place of the alkyl derivative gave instead, N-acyl phosphorimides.[10-15] More recently, α-aminocarboxylic esters were produced from base-catalyzed rearrangement of N-chlorimidates containing α hydrogen.[6] This paper describes the condensation of sulfides and mercaptans with N-chlorobenzimidates.

Methyl N-chlorobenzimidate (**1**) and methyl N-chloro-*p*-methoxybenzimidate (**2**) were most conveniently prepared by the sodium hypochloride procedure of Stieglitz[1] from their corresponding benzimidate hydrochloride salts in 80 and 70% yield, respectively.

Because compounds of type **1** and **2** were poorly identified by the early workers, some effort was devoted to establish further their structural identity. Both N-chloro compounds (**1** and **2**) were shown by nmr spectroscopy to be a mixture of isomers in which the OCH_3 and the Cl groups on an imine double bond are in *syn* and *anti* configuration. Assignments were made based on extension of the generalization for ethylenes (C=C) where it is known that protons *cis* (*syn*) to an electronegative group appear further downfield than *trans*(*anti*). Compound **1** was a 9:1 mixture of *syn* (δ 3.85 ppm) and *anti* (δ 3.65 ppm) isomers. Heating **1**



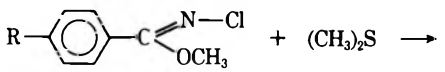
1 (*syn*)



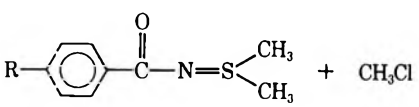
1 (*anti*)

for 40 min at 100° produced an equilibrium mixture at 7.5:2.5 of *syn* to *anti* isomers, respectively. Compound **2** was a 3.7:1.3 mixture of *syn* (δ 3.87 ppm) and *anti* (δ 3.72 ppm), isomers, respectively. In the present work no separation of the isomeric products was attempted. Further analytical data supporting the assigned structures are presented in the Experimental Section.

Methyl N-chlorobenzimidate (**1**) reacted readily with methyl sulfide giving S,S-dimethyl-N-benzoylsulfilimine, **3** (72%), and methyl chloride and thus furnishing a fifth general route to dialkylsulfilimines.[16]

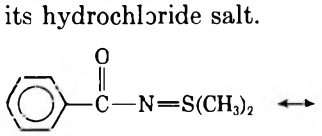


1, R = H
2, R = CH_3O



3, R = H
4, R = CH_3O

Similarly compound **2** gave S,S-dimethyl-N-(*p*-methoxybenzoyl)sulfilimine (**4**) in 65% yield. The reactions were exothermic when the starting materials were mixed at room temperature and methyl chloride was liberated. The extent of reaction was followed by methyl chloride evolution as the mixtures were finally heated to complete the reaction. The sulfilimine products were water soluble, colorless solids and insensitive to hydrolysis at room temperature. Boiling water caused partial hydrolysis to the benzamide. Assignment of structures was based on elemental analysis and infrared and nmr spectral data. The structure of **3** was further characterized by the formation and analysis of its hydrochloride salt.

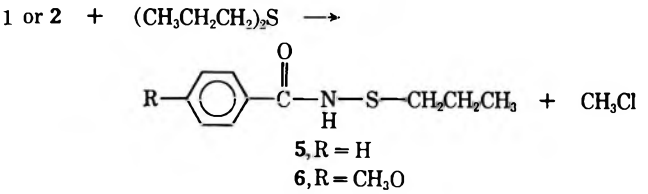


When *n*-propyl sulfide was employed in place of methyl sulfide, under identical reaction conditions, the

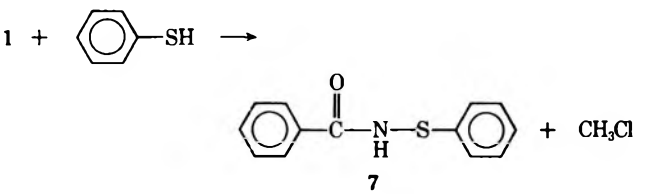
(1) J. Stieglitz, *Amer. Chem. J.*, **18**, 751 (1896).
(2) J. Stieglitz and R. B. Earle, *ibid.*, **30**, 399 (1903).
(3) W. S. Hilpert, *ibid.*, **40**, 150 (1908).
(4) J. Houben and E. Schmidt, *Ber.*, **46**, 3616 (1913).
(5) H. S. Wheeler and P. T. Walden, *Amer. Chem. J.*, **19**, 129 (1897).
(6) H. E. Baumgarten, H. E. Dirks, J. M. Petersen, and R. L. Zey, *J. Org. Chem.*, **31**, 3708 (1966).
(7) J. Stieglitz and E. E. Slosson, *Ber.*, 1613 (1901).
(8) G. I. Derkach, A. M. Lepesa, and A. V. Kirsanov, *J. Gen. Chem. USSR*, **32**, 167 (1962).
(9) K. A. Petrov, A. A. Neimysheva, M. G. Fomenko, L. M. Chemushevich, and A. D. Kuntsevich, *ibid.*, **31**, 516 (1961).
(10) G. I. Derkach, E. S. Gubnitskaya, V. A. Shokol, and A. V. Kirsanov, *ibid.*, **32**, 1201 (1962).
(11) G. I. Derkach, E. S. Gubnitskaya, V. A. Shokol, and A. V. Kirsanov, *ibid.*, **32**, 1874 (1962).
(12) G. I. Derkach, E. S. Gubnitskaya, L. J. Samarai, and V. A. Shokol, *ibid.*, **33**, 557 (1963).
(13) G. I. Derkach, G. K. Fedorova, and E. S. Gubnitskaya, *ibid.*, **33**, 1017 (1963).
(14) G. I. Derkach and L. J. Samarai, *ibid.*, **34**, 1161 (1964).
(15) G. I. Derkach and E. S. Gubnitskaya, *ibid.*, **35**, 1009 (1965).

(16) Synthesis of sulfilimines are described in the following references: (a) C. R. Johnson and J. J. Rigau, *J. Org. Chem.*, **33**, 4340 (1968); (b) L. Horner and A. Christmann, *Chem. Ber.*, **96**, 388 (1963); (c) C. King, *J. Org. Chem.*, **25**, 352 (1960); (d) D. S. Tarbell and C. Weaver, *J. Amer. Chem. Soc.*, **63**, 2939 (1941); (e) F. G. Mann and W. J. Pope, *J. Chem. Soc.*, **121**, 1052 (1922); (f) F. G. Mann, *ibid.*, 958 (1932).

sulfilimines were not obtained. Instead C–S bond cleavage resulted to give sulfenamides **5** and **6** and methyl chloride in quantitative yield. The structure of solid sulfenamides was confirmed by elemental analysis and infrared and nmr spectral data.

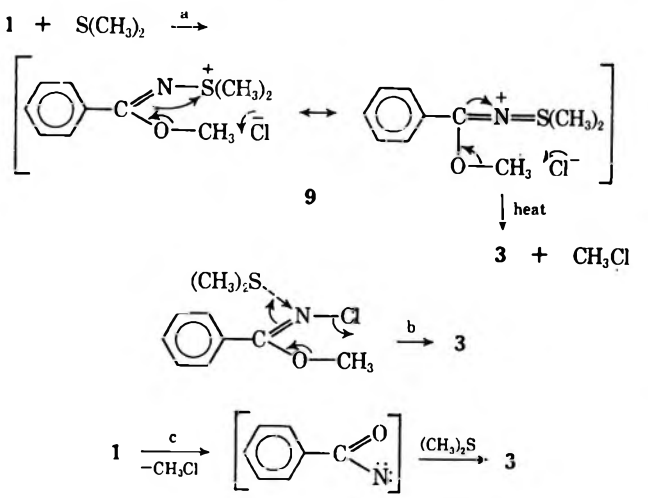


An attempt to prepare authentic **5** from the reaction of *n*-propyl mercaptan and **1** gave, instead, the oxidation product, *n*-propyl disulfide, and by-product methyl benzimidate hydrochloride as the only identified products, each in about 55% yield. On the other hand, a rapid and exothermic reaction occurred when phenyl mercaptan was used in place of the alkyl mercaptan. Thus, N-benzoylbenzenesulfenamide (**7**) was obtained in 60% yield.



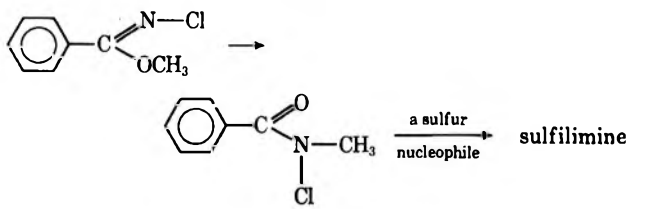
Attempts to employ an aromatic sulfide in place of the alkyl sulfides in reactions leading to products similar to **3** and **4** were unsuccessful. Instead, reaction of **1** with diphenyl sulfide at temperatures up to 193° gave N-benzoyl-N′-phenylurea as the only isolable product in very low yield while at room temperature only methyl benzimidate hydrochloride was identified. *n*-Propyl disulfide reacted with **1** with explosive violence. Heating a mixture of **1** and elemental sulfur also caused a sudden uncontrollable violent reaction. Both of these reactions gave product mixtures which were not completely separated and identified.

Detailed mechanisms for the formation of sulfilimines are not clear. One can postulate (a) an initial salt formation (**9**) which then loses methyl chloride to give product or (b) a concerted process involving product formation with simultaneous loss of methyl chloride and (c) formation of a nitrene intermediate.



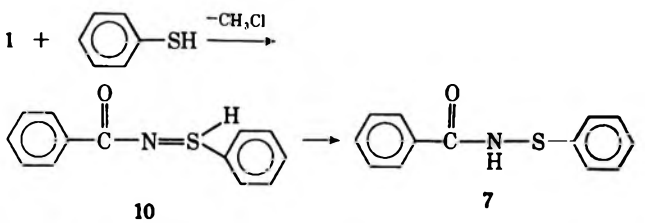
Although nitrene intermediates cannot be entirely excluded, the probability of their involvement is not favorable since reaction products of these species were not found by either thermolysis of **1** and **2** in cyclohexene[17–19] or treatment of mixtures of **1** and **2** in cyclohexene with dimethyl sulfide. Between the two remaining pathways (a and b), there is no absolute way of distinguishing one over the other. It is of interest that the reaction mixtures exhibited an increase in viscosity immediately after mixing the sulfide and N-chlorobenzimidates and that the sulfides were not boiled out of the reaction mixtures during heating.

A mechanism involving prior formation of a N-chlorobenzamide from the N-chlorobenzimidate in a Chapman-type rearrangement with subsequent α-elimination processes appears unlikely in view of the



overall low temperatures of the reactions described here and the stability of the N-chlorobenzimidates toward high temperatures as seen in the nmr study.

Formation of the sulfenamide from phenyl mercaptan and **1** could have involved rearrangement of the unusual sulfilimine (**10**). This compound is representative of an unknown class of compounds and it could well be postulated that in such structural circumstances a tendency toward molecular rearrangement for the sulfur atom to exist in its more stable divalent would prevail.



The mechanism of C–S bond cleavage when *n*-propyl sulfide was employed in the reaction is unclear, and the fate of the fragmented propyl group has not been established. However, propane and propylene derivatives were not found (by mass spectrometry) in the gaseous product.

Experimental Section

Methyl Benzimidate Hydrochloride.—The procedure employed was basically that of Pinner.[20,21] Extreme care was taken to maintain anhydrous conditions for the preparation and handling of this compound. Dry gaseous hydrogen chloride (58.5 g, 1.6 mol) was bubbled into a mixture of benzonitrile (154.5 g, 1.5 mol) and anhydrous methanol (57.7 g, 1.8 mol) during about 4 hr while the reaction temperature was maintaind at −5 to 0°. When the addition was complete, the reaction mixture was held at 0° for 3 days. The crystallized product was filtered quickly

(17) D. Saika and D. Swern, *J. Org. Chem.*, **33**, 4548 (1968).
(18) R. J. Cotter and W. F. Beach, *ibid.*, **29**, 751 (1964).
(19) D. S. Breslow, E. I. Edwards, R. Leone, and P. von E. Schleyer, *J. Amer. Chem. Soc.*, **90**, 7097 (1968).
(20) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).
(21) A. Pinner, "Die Imidoather und ihre Derivate," Oppenheim, Berlin, 1892.

in a nitrogen atmosphere, washed thoroughly with ether, and dried in a vacuum desiccator over sodium hydroxide pellets to yield 163.5 g (64%) of pure salt, mp 103.5–104° (gas evolution) (lit.[22] mp 105°). Crystallization from chloroform–benzene did not change the melting point.

Methyl N-Chlorobenzimidate (1).—The chlorination procedure employed was a modification of that of Stieglitz.[1] To a freshly prepared solution of sodium hypochlorite [prepared by adding gaseous chlorine (218 g, 3.08 mol) to a solution of sodium hydroxide (176 g, 4.4 mol) in 1055 g of water at 0°] was added 300 ml of 1,1,2-trichloro-1,2,2-trifluoroethane (UCON-113). To the resulting mixture was added portionwise 150 g (0.88 mol) of crude methyl benzimidate hydrochloride over 20 min while keeping the reaction temperature at 0–5°. When the addition was complete, the reaction mixture was stirred at 0–5° for 10 min, the layers were separated, and the aqueous layer was extracted three times with 50-ml portions of UCON-113. The combined UCON-113 extracts were dried over anhydrous $MgSO_4$ for 1 hr, filtered, and evaporated to give a colorless oil. Distillation afforded 121 g (81%) of colorless product 1, bp 118–120° (15.0 mm).

Anal. Calcd for C_8H_8ClNO: C, 56.65; H, 4.75; Cl, 20.90; N, 8.26. Found: C, 56.70; H, 4.64; Cl, 21.90; N, 8.25.

The infrared absorption spectrum revealed bands at 6.15 (C=N) and 9.68 μ (O–CH_3). The nmr spectrum ($CDCl_3$) exhibited two singlets in a 9:1 ratio at δ 3.85 and 3.65 ppm, respectively, attributed to the methyl protons, and a multiplet centered at δ 7.34 ppm for the phenyl ring protons. Raising the temperature from 25 to 70° altered the methyl proton ratio of the low-field to high-field singlets to 8.5:1.5, respectively. A 7.5:2.5 equilibrium mixture of the 3.85 to 3.65 ppm singlets, respectively, was obtained after 40 min at 100°.

Methyl *p*-Methoxybenzimidate Hydrochloride.—The preparation of this hydrochloride was carried out by the same procedure as described for the preparation of methyl benzimidate hydrochloride. From 199.7 g (1.5 mol) of anisonitrile, 57.7 g (1.8 mol) of anhydrous methanol, and 58.5 g (1.6 mol) of hydrogen chloride there was obtained 263 g (87%) of crude, dried white crystalline product. This material was used without purification in the subsequent chlorinations.

Methyl N-Chloro-*p*-methoxybenzimidate (2).—To a 2.8 to 3.0 *M* solution of sodium hypochlorite [prepared by adding 70 g (2.0 mol) of chlorine to a solution of 80 g (2 mol) of sodium hydroxide in 250 g of water while keeping the temperature at 0–5°] was added 300 ml of UCON-113, and gradually 263 g (1.30 mol) of crude methyl *p*-methoxybenzimidate hydrochloride during 15 min while maintaining the temperature at 0–5°. The resulting mixture was stirred for 30 min after the addition of the salt was complete, the layers were separated, and the aqueous layer was extracted with three 50-ml portions of UCON-113. The combined UCON-113 extracts were dried over anhydrous $MgSO_4$ for 1 hr, filtered, and evaporated to give a crude colorles oil. Distillation gave 178.5 g (69%) of product, bp 94.5–107° (0.025–0.050 mm). Redistillation afforded 137.2 g (53%) of pure product: bp 95.5–99° (0.18–0.20 mm); ir 6.18 (conjugated C=N) and 9.67 μ (O–CH_3); nmr ($CDCl_3$) δ 7.63 (m, 2 H, aromatic), 6.87 (m, 2 H, aromatic), 3.72 (s, 3 H, $CH_3OC_6H_4$), and two singlets at 3.87 and 3.72 ppm (3 H) from the *syn* and *anti* forms in an 87.4 to 12.6 ratio, respectively, at 25°.

Anal. Calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; Cl, 17.76; N, 7.02. Found: C, 54.44; H, 5.27; Cl, 17.57; N, 7.00.

S,S-Dimethyl-N-benzoylsulfilimine (3).—Methyl N-chlorobenzimidate (17.0 g, 0.1 mol) was added dropwise to a stirred solution of 6.21 g (0.1 mol) of methyl sulfide in 10 ml of benzene while keeping the temperature at 30–35°. When the addition was complete, the mixture was heated to 75° during 2 hr. The next day additional methyl sulfide (2.7 g, 0.044 mol) was added and the reaction mixture was heated at 55° for 1 hr. During this time 1520 ml (68%) of methyl chloride was collected and identified by mass spectrometry. The solvent and excess methyl sulfide were evaporated by means of a stream of nitrogen gas, the crude white product was washed successively with 20 ml of petroleum ether and 20 ml of benzene, and dried to yield 13.0 g (72%), mp 106.5–108.5°. Recrystallization from benzene raised the melting point to 107.5–108.5°; ir (KBr) 6.25, 6.67 (aromatic C=C), 6.44 (C=O), 7.50 (N=S), and 7.66 μ (S–CH_3); nmr ($CDCl_3$) δ 2.62 (s, 6 H, $(CH_3)_2S<$), 7.33 (m, 3 H, aromatic), and 8.06 ppm (m, 2 H, aromatic).

(22) M. J. Hunter and M. S. Ludwig, *J. Amer. Chem. Soc.*, **84**, 3491 (1962).

Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73; S, 17.69. Found: C, 60.37; H, 6.20; N, 7.77; S, 17.65.

S,S-Dimethyl-N-benzoylsulfilimine Hydrochloride.—The hydrochloride was prepared by saturating a solution of 2.5 g (0.014 mol) of S,S-dimethyl-N-benzoylsulfilimine in 50 ml of benzene with hydrogen chloride gas at ambient temperature. The reaction mixture was allowed to stand for 2 hr and then filtered. The white product was washed with two 20-ml portions of ether and dried to yield 2.52 g (84%), mp 180–182°. Recrystallization from ethanol afforded 2.14 g (71%), mp 180–182°; ir 3.30–3.80 (salt), 5.88 (C=O), and 7.05 μ (N=S); nmr (D_2O) δ 3.50 (s, 6 H, $(CH_3)_2S<$), 4.85 (s, 1 H, $=N<_H$), and 7.83 ppm (m, 5 H, aromatic).

Anal. Calcd for $C_9H_{12}ClNOS$: C, 49.63; H, 5.55; Cl, 16.28; N, 6.43; S, 14.72. Found: C, 49.93; H, 5.57; Cl, 16.12; N, 6.53; S, 14.40.

Reaction of Methyl N-Chlorobenzimidate with *n*-Propyl Sulfide.—*n*-Propyl sulfide (11.8 g, 0.1 mol) was added to 17.0 g (0.1 mol) of methyl N-chlorobenzimidate over a period of 20 min while maintaining the temperature at 25–30°. There was a strong exotherm of reaction, and during this time methyl chloride (identified by mass spectrometry) commenced to be liberated and was collected over water. The mixture was stirred and gradually heated to 134° until (about 4 hr) 1 mol of methyl chloride per mol of starting N-chloro compound had been collected. After cooling the reaction mixture, the crude **N-benzoyl-1-propanesulfenamide** (5, 19.3 g, 100%) was extracted with four 500-ml portions of boiling petroleum ether (63–75°) to yield 6.0 g (36%). An analytical sample was prepared by crystallization from benzene–cyclohexane: mp 70–73°; ir 3.01 (N–H), 6.0 (C=O), and 7.9 μ (S–CH_2); nmr ($CDCl_3$) δ 0.98 (t, 2 H, SCH_2CH_2-), 1.63 (sextet, 2 H, $-CH_2CH_2CH_3$), 2.78 (t, 3 H, $-CH_2CH_3$), 7.39 (m, 3 H, aromatic), 7.60 (s, 1 H, –NH–), and 7.84 ppm (m, 2 H, aromatic).

Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.83; H, 6.61; N, 7.44.

Reaction of Diphenyl Sulfide with Methyl N-Chlorobenzimidate.—A mixture of 5.7 g (0.031 mol) of diphenyl sulfide and 8.45 g (0.05 mol) of methyl N-chlorobenzimidate was slowly heated to a maximum temperature of 193° during 7 hr. A total of 350 ml of methyl chloride was collected. The black tarry-appearing reaction mixture was filtered and a black solid was collected, washed with 20 ml of a 1:1 mixture of benzene–cyclohexane, and dried to yield 0.40 g (6.7%), mp 183–190° dec. The crude gray product was purified by two recrystallizations from benzene to yield 0.10 g (1.7%) of **N-benzoyl-N'-phenylurea**, mp 197–199° dec. The ir and nmr spectra were identical with that of an authentic sample of the urea product.

Reaction of Methyl N-Chlorobenzimidate with Benzenethiol.—Benzenethiol (5.51 g, 0.05 mol) was added dropwise to a solution of 8.45 g (0.05 mol) of methyl N-chlorobenzimidate in 5 ml of benzene during 1 hr with cooling to maintain the temperature at 25–30°. The resulting reaction mixture was then slowly heated to 81° in 3 hr. During this time 670 ml (60%) of methyl chloride was collected. The solid brown residue product was washed with three 15-ml portions of cold benzene and dried to yield 6.9 g (60%) of white **N-benzoylbenzenesulfenamide** (7), mp 87–90°. An analytical sample was prepared by recrystallization from benzene to yield 5.5 g (48%), mp 95–97°: ir 3.05 (N–H), 6.00 (C=O), 6.74 (N–H), 9.10 (S–C_6H_5), and 9.67 μ (S–C_6H_5); nmr ($CDCl_3$) δ 8.05 (s, 1 H, –NH–), 7.86 (m, 2 H, aromatic), and 7.32 ppm (m, 8 H, aromatic).

Anal. Calcd for $C_{13}H_{11}NOS$: C, 68.10; H, 4.84; N, 6.11; S, 13.98. Found: C, 68.35; H, 5.04; N, 6.41; S, 13.20.

S,S-Dimethyl-N-(*p*-Methoxybenzoyl)sulfilimine (4).—Methyl sulfide (6.83 g, 0.11 mol) was added dropwise to 20.0 g (0.10 mol) of methyl N-chloro-*p*-methoxybenzimidate with stirring. The addition was complete in 10 min and during this time the temperature rose from 25 to 35° and 60 ml of methyl chloride was collected. The mixture was slowly heated to 64° during 4.5 hr. After cooling, 10 ml of benzene and an additional 0.62 g (0.01 mol) of methyl sulfide was introduced, and the reaction mixture was heated for 4 hr at 85–88° until gas evolution was complete. The solid product was washed successively with 20 ml of petroleum ether (63–75°) and two 30-ml portions of diethyl ether and dried to yield 13.76 g (65%), mp 87–92°. Recrystallization from benzene gave 12.30 g (58%), mp 87.5–92°. An analytical sample was prepared by two recrystallizations from benzene, mp 95–99°: ir (KBr) 3.50 (O–CH_3), 6.23 (C=O), 6.30, 6.46, 6.54, 6.62, 6.75 (aromatic C=C), 7.50 (N=S),

8.04 (O-C_6H_4), 9.60, and 9.80 μ (O-CH_3); nmr ($CDCl_3$) δ 2.73 (s, 6 H, =S(CH_3)$_2$, 3.82 (s, 3 H, -OCH_3), 6.85 (d, 2 H, aromatic), and 8.03 ppm (d, 2 H, aromatic).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; S, 15.18. Found: C, 56.54; H, 5.92; N, 6.70; S, 14.86.

N-(*p*-Methoxybenzoyl)-1-propanesulfenamide (6).—*n*-Propyl sulfide (5.91 g, 0.05 mol) was added to 10 g (0.05 mol) of methyl N-chloro-*p*-methoxybenzimidate during 10 min. There was only very slight exotherm of reaction (2° rise) and no gas evolved under these conditions. The resultant reaction mixture was slowly heated to 135° during 3.5 hr and maintained at 135–137° temperature for 2.0 hr. During this time the theoretical quantity (1120 ml) of methyl chloride (identified by mass spectrometry) had been collected. The reaction product was filtered to give a tacky, pale yellow solid which was washed with cyclohexane and dried to yield 11.30 g (100%). This product was extracted with five 400-ml portions of boiling petroleum ether (63–75°). The yellow insoluble amorphous residue was discarded and the extracts were allowed to stand for 2 days. The crystallized product was collected by filtration and dried to yield 3.45 g (31%), mp 86.5–89°. An analytical sample was prepared by recrystallization of 0.5 g from 200 ml of petroleum ether (63–75°): yield 0.43 g; mp 92–93.5°; ir (KBr) 3.05 (N-H), 3.52 (O-CH_3), 6.08 (amide C=O), 6.24, 6.36, and 6.66 μ (aromatic C=C); nmr ($CDCl_3$) δ 0.99 (t, 2 H, -SCH_2CH_2-), 1.64 (sextet, 2 H, -$CH_2CH_2CH_3$), 2.79 (t, 3 H, -CH_2CH_3), 3.82 (s, 3 H, CH_3-OC_6H_4-), 6.89 (m, 2 H, aromatic), 7.45 (s, 1 H, -NH-), and 7.82 ppm (m, 2 H, aromatic).

Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.62; H, 6.74; N, 6.42.

Registry No.—1 *syn*, 23632-48-6; 1 *anti*, 23632-47-5; 2 *syn*, 24978-55-0; 2 *anti*, 25024-02-6; **3**, 19397-91-2; **3** (HCl), 24978-57-2; **4**, 25024-03-7; **5**, 24978-58-3; **6**, 24978-59-4; **7**, 23847-33-8.

Nucleophilic Scission of Disulfides by Selenolate. Synthesis and Some Properties of Acyclic Thiolselenenates[1,2]

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Various types of compounds possessing a sulfur–sulfur bond, *e.g.* diaryl disulfides (ArSSAr), dialkyl disulfides (RSSR), sulfenyl thiocyanates (RSSCN), sulfenyl sulfites ($RSSO_3^-$), and sulfenyl thiosulfates ($RSS_2O_3^-$), are susceptible to nucleophilic attack.[3] The ionic scission of sulfur–sulfur bonds by nucleophilic agents has been repeatedly investigated and, on the basis of kinetic studies, appears to involve an S_N2 mechanism.[4]

This paper describes the scission of disulfides by selenolate. As an *a priori* consideration, this type of reaction would be expected to proceed readily. On the one hand the valence shell electrons of selenium are highly polarizable,[5] resulting in highly nucleophilic species;[6,7] on the other hand sulfur in a disulfide bridge is capable of using the empty 3d orbitals in the transition state, facilitating nucleophilic scission of S–S bonds.[4] Added interest in this type of reaction stemmed from a possible general application of this method for the synthesis of thiolselenenates, particularly those which are aliphatic and acyclic in nature; it appears that the first compound of this type, *viz.* 1-amino-3-selena-4-thiatetradecane, was prepared only recently.[8]

In this study 2-naphthylsulfenylthiocyanate (**2**),[9] a relatively stable compound among the labile sulfenylthiocyanates, was allowed to react with the selenolate of N-carbobenzoxy-L-selenocysteine diphenylmethyl ester (**1**);[10] the thiolselenenate (**3**) was isolated in moderate yield following chromatographic separation from the diselenide (**4**) and disulfide (**5**) (Scheme I). In independent experiments it was noticed that **2** is rather labile in an alkaline medium giving rise to the disulfide **5**; since it was felt that the moderate yield of **3** may have been associated with the lability of the substrate **2**, experiments were repeated using increasing amounts of **2** (up to 3 mol equiv). The fact that neither the yield of **3** nor the ratio of **3** to **4** were changed indicated that the moderate yield of product could be due to an intrinsic instability of **3**, a possibility in line with earlier observations with thiolselenenates.[8,11]

In order to eliminate definitively possible interference by a base-labile substrate, **2** was replaced with the more stable sulfenyl sulfite (Bunte salt); pure unsymmetrical disulfides have been prepared in weakly alkaline reaction media using sulfenyl sulfites.[12] However, when the anion **1** treated with sodium S-benzylthiosulfate (**6**)[13] the desired thiolselenenate (**7**) was isolated only in somewhat higher yield (Scheme II). This again pointed to an instability of the thiolselenenate.

Further semiquantitative studies with **3** and **7** involving solvent variation *per se* showed that disproportionation takes place, the rate depending in first approximation on the polarity of the solvent. Essentially, instantaneous disproportionation of **3** and **7** occurs in basic media and a rapid disproportionation also takes place in acidic media as illustrated by the attempt to decarbobenzoxylate **3** which resulted in L-selenocystine. From these and other findings[8,11] it appears that aliphatic acyclic thiolselenenates are exceedingly reactive molecules, while cyclic thiolselenenates are generally more stable,[14–16] although excep-

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(2) The following abbreviations have been adopted: Z = $C_6H_5CH_2OCO$, DMF = N,N-dimethylformamide, AcOH = acetic acid, EtOH = ethanol, MeOH = methanol, Et_2O = diethyl ether, EtOAc = ethyl acetate.

(3) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(4) O. Foss, "Organic Sulfur Compounds," Vol. I, Pergamon Press, London, 1961, p 83.

(5) G. Bergson, *Ark. Kemi*, **13**, 11 (1958).

(6) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 141 (1953).

(7) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," New York, N. Y., 1941, p 423.

(8) D. L. Klayman, *J. Org. Chem.*, **30**, 2454 (1965).

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(10) J. Roy, Wolfgang Gordon, I. L. Schwartz, and R. Walter, *J. Org. Chem.*, **35**, 510 (1970).

(11) G. Bergson and G. Nordström, *Ark. Kemi*, **17**, 569 (1961).

(12) A. Schöberl and G. Bauer, *Angew. Chem.*, **69**, 478 (1957); *Fette Seifen*, **60**, 1061 (1958).

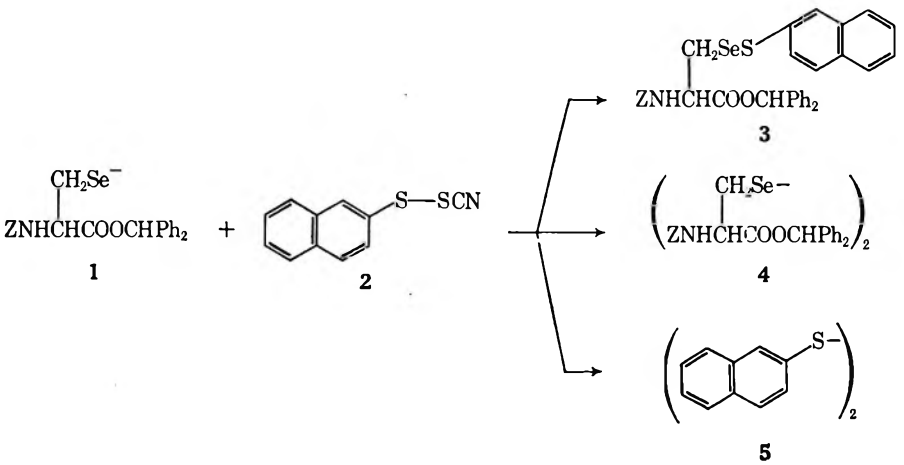
(13) T. S. Price and D. F. Twiss, *J. Chem. Soc.*, **95**, 1489 (1909).

(14) G. Bergson and A. Biezais, *Ark. Kemi*, **18**, 143 (1961).

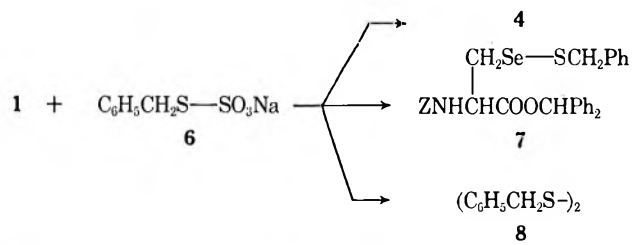
(15) R. Walter and V. du Vigneaud, *J. Amer. Chem. Soc.*, **87**, 4192 (1965); **88**, 1331 (1966).

(16) R. Walter, First American Peptide Symposium at Yale University, Conn., Aug 1968; B. Weinstein, Ed., "Chemistry and Biochemistry," Marcel Dekker, New York, N. Y., 1970, p 467.

SCHEME I



SCHEME II



tions are encountered.[17] If thiolselenenates occur in living organisms, their high reactivity would dictate that their existence would be transient. Hence, one would expect to find thiolselenenates to be involved in catalytic processes rather than as a permanent component of protein structures.

Experimental Section[18]

N-Carbobenzoxy-Se-(naphthyl-2-thio)-L-selenocysteine Diphenylmethyl Ester (3).—Sodium (0.107 g) was dissolved in EtOH (5 ml); the resulting solution was degassed and all subsequent steps were performed under hydrogen atmosphere. To the solution, saturated with hydrogen selenide gas, N-carbobenzoxy-O-tosyl-L-serine diphenylmethyl ester[19] (1.86 g) dissolved in 5 ml of degassed DMF was added. The reaction mixture was stirred for an additional 0.5 hr and NaOH (0.17 g) dissolved in 1 ml of degassed water was then added, immediately followed by 2-naphthylsulfenyl thiocyanate (2)[9] (1.8 g) in degassed DMF (5 ml). The reaction was exothermic and the mixture turned dark and solid separated. Stirring was continued for 3 hr, and the reaction mixture was subsequently diluted with EtOAc (80 ml) and shaken thoroughly with water (30 ml); at this stage 0.4 g of 2-naphthyl disulfide, mp 138–139° (lit.[9] mp 139–140°), which was insoluble in both the aqueous and organic phases, was isolated by filtration. From the filtrate the aqueous layer was separated and the organic layer was washed with three 25-ml portions of water, dried, and evaporated to dryness under vacuum. The residual semisolid was dissolved in a minimum volume of boiling EtOAc; on standing a second batch of 2-naphthyl disulfide separated as crystalline yellow solid to yield 0.5 g, mp 138.5–139.5°. The filtrate, after separation of this solid, was then evaporated under vacuum and the viscous mass was tested on silica gel G tlc in the solvent system EtOAc:C_6H_6 (1:9, v/v). Two spots, Zahn's reagent[20] positive (the one spot with the higher R_f value was later found to correspond to **3**, see below; the R_f value of the other spot was identical with that of authentic **4**)[10] and one Zahn's reagent negative spot (a pronounced white spot with an R_f value corresponding to authentic **5**) were detected. Compound **3** was eluted from a silica gel G column with C_6H_6 containing 1.5% EtOAc and crystallized from EtOAc–MeOH in clusters of fine needles: yield 0.5 g (24%); mp 85.5–86.5°; $[\alpha]^{30.6}D$ −75.0° (2% in DMF).

Anal. Calcd for $C_{34}H_{29}NO_4SSe$: C, 65.2; H, 4.66; N, 2.24. Found: C, 65.2; H, 4.66; N, 2.22.

N-Carbobenzoxy-Se-(benzylthio)-L-selenocysteine Diphenylmethyl Ester (7).—Sodium hydrogen selenide was prepared from sodium (0.107 g) dissolved in absolute EtOH (5 ml). Under hydrogen atmosphere N-carbobenzoxy-O-tosyl-L-serine diphenylmethyl ester (1.86 g) in degassed DMF (5 ml) was added and stirring was continued for 0.5 hr. Base (0.17 g of NaOH dissolved in 1 ml of degassed water) was added, followed by sodium S-benzylthiosulfate (6)[13] (2.26 g) in 3 ml of degassed water. The reaction mixture, after stirring under hydrogen for 3 hr, was diluted with EtOAc (80 ml) and washed with four 25-ml portions of water. The organic layer was separated and dried, and the solvent was removed under reduced pressure. The resulting oil was chromatographed on a silica gel G column and three fractions were collected. The first fraction eluted with C_6H_6 containing 1% EtOAc, yielded upon evaporation a solid which after crystallization from 95% EtOH was identified as benzyl disulfide (8), 0.5 g, mp 69–70° (lit.[21] mp 69–70°). The second fraction eluted with C_6H_6 containing 2% EtOAc, also gave a crystalline solid upon evaporation of solvent. Recrystallization from an EtOAc–EtOH mixture gave **7** in 36% yield (0.7 g), mp 74–75°, $[\alpha]^{30.5}D$ −57.0° (2% in DMF).

Anal. Calcd for $C_{31}H_{29}NO_4SSe$: C, 63.0; H, 4.95; N, 2.37. Found: C, 63.0; H, 5.08; N, 2.32.

The third fraction eluted with C_6H_6 containing 3% EtOAc, was identified as bis(diphenylmethyl)bis(N-carbobenzoxy) L-selenocystinate (4) after crystallization from an EtOAc–EtOH mixture; yield, 0.85 g, mp 101–102° (lit.[10] mp 101–102°); in addition the ir spectra taken in KBr were superimposable.

L-Selenocystine.—The thiolselenenate **3** (0.25 g) was dissolved in dry AcOH (1 ml) and 4 *N* HBr in AcOH (1 ml) was added while stirring. After 15 min the reaction mixture was diluted with anhydrous Et_2O (25 ml) and chilled, and the solid precipitate was filtered and washed with a small volume of cold anhydrous Et_2O. The solid was suspended with 2 ml of water and the insoluble material was collected by filtration (this material was identified by melting point and ir as 2-naphthyl disulfide). The pH of the filtrate was adjusted to 5 whereupon a yellow solid separated which was collected by filtration, washed with a small volume of water, and dried *in vacuo* over P_2O_5 to yield 0.05 g (75%). On the basis of melting point, superimposable ir, and specific optical rotation the material was identified as L-selenocystine.[10]

(17) G. Bergson, *Ark. Kemi*, **19**, 75 (1962).

(18) All melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected. The infrared spectra were recorded on a Perkin-Elmer 457 infrared spectrophotometer in pressed disks of KBr at a concentration of 0.3%. The optical rotations were determined with a Carl Zeiss photoelectric precision polarimeter (0.005°). The elementary analyses were carried out by Galbraith Laboratories, Knoxville Tenn.

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(20) H. Zahn and E. Rexroth, *Z. Anal. Chem.*, **148**, 181 (1955).

(21) "Dictionary of Organic Compounds," Vol. 2, Oxford University Press, New York, N. Y., 1965, p 904.

Registry No.—3, 24978-13-0; 7, 24978-14-1.

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Solvent Modification in Merrifield Solid-Phase Peptide Synthesis

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Occasionally during the use of Merrifield solid-phase peptide synthesis from seemingly simple syntheses, steps occur where part of the peptide chain stops growing.[2-5] We encountered such a step at glutamine during the synthesis of the peptide H_2N-Ser-Arg-Phe-Gly-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Ser-Pro-Phe-Gly-Lys-COOH.[6] Although the use of trifluoroacetic acid[2] and double couplings[4] in two different solvents improved our synthesis somewhat, the use of a mixed solvent system of methylene chloride and dimethylformamide (DMF) gave the best results for our peptide. We interpret this to mean that our step was caused by a tertiary structure peculiar to this peptide, and we suggest that this solvent system may be generally useful for problems of this type.

Table I shows the results of several experiments using a variety of deblocking agents, coupling reagents, and reaction times. Each experiment was run in triplicate. Figure 1 is a graphic interpretation of Table I. Only the first five residues, HOOC-Lys-Gly-Phe-Pro-Ser-NH_2, could be completely coupled using methylene chloride as the solvent for dicyclocarbodiimide (DCCI), even when trifluoroacetic acid in methylene chloride was used for deblocking. Only 70% of the sixth amino acid, glutamine, could be added as an active ester in DMF within 6 hr. However, if 1.5 *M* of urea was added to DMF, glutamine could be added to an extent of 90% after 6 hr and the reaction was complete after 24 hr. If DMF ($^1/_3$ by volume) was added to the DCCI–methylene chloride couplings and allowed to react 6 hr, glycine (7th), glutamic acid (8th), and alanine (9th) could be coupled completely. If only DCCI–methylene chloride was used, just 50% of the chain continued to grow. Knowing this, amino acids 6 through 13 were coupled using DMF while it was not necessary for the coupling of the remaining three amino acids.

It should be mentioned that Merrifield,[2] while showing the usefulness of trifluoroacetic acid, actually used DCCI with DMF and methylene chloride as solvents in adding histidine while making bradykinin, since

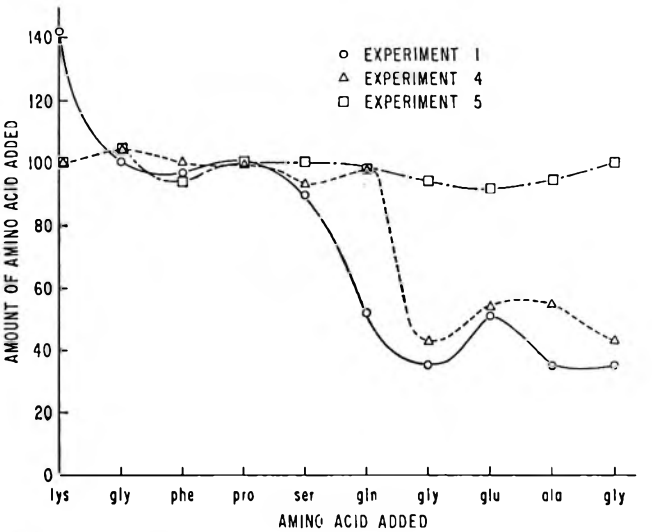

Figure 1.—Graphical interpretation of experiments 1, 4, and 5.

histidine was partly dissolved in DMF for the coupling. It appears that while deblocking with trifluoroacetic acid can overcome many of the chain-termination problems in peptide synthesis, the combination of deblocking with trifluoroacetic acid and coupling with DCCI in DMF and methylene chloride might prove more satisfactory.

Experimental Section

Dry chloromethylated copolystyrene–2% divinylbenzene (20 g) (Biorad Beads S-X-2, 200–400 mesh, capacity 1.1 milliequiv/g) was mixed with 20 mmol of both triethylamine and *e*,N-carbobenzoxy-*a*,N-*t*-butoxylysine in 80 ml of ethanol. The mixture was refluxed for 46 hr. The resin was washed in ethanol, methylene chloride, water and methanol and then dried. The resin contained 0.2 mmol of blocked lysine per gram of resin. The following cycle of deprotection, neutralization, and coupling was carried out on 1 g of resin with a total solution volume of 10 ml for each residue added: (1) three washes with the deprotecting solvent–acetic acid, propionic acid, or methylene chloride; (2) 30 min of reacting with the deprotecting agent—acetic acid and 1 *M* HCl, propionic acid and 0.8 *M* HCl, both with 1% by volume mercaptoethanol, or 50% trifluoroacetic acid in 50% methylene chloride with 5% by volume mercaptoethanol;[7] (3) three washes with the deprotecting solvent—acetic acid, propionic acid, or methylene chloride; (4) two washes with ethanol; (5) three washes with chloroform; (6) neutralization for 10 min with a mixture of 12.5% by volume of triethylamine and 87% by volume of chloroform; (7) three washed with chloroform; (8) three washes with methyl chloride if DCCI coupling or three washes with DMF if active ester coupling; (9) the coupling step depended upon the experiment and the amino acid being added as shown in Table I. It consists of one of the following procedures: (A) addition of 5 ml of methylene chloride containing 2.2 mmol of blocked amino acid and equilibration for 10 min, (B) addition of 5 ml of a solution of DMF and methylene chloride (60:40) containing 2.2 mmol of blocked amino acid with 10 min of equilibration time, or (C) addition of 10 ml of DMF containing 1.5 *M* urea with 4 mmol of the active ester of glutamine; (10) addition of 3 ml of DCCI (66 gm DCCI/400 ml of methylene chloride) followed by 2 ml of methylene chloride. This step is not performed for active ester additions. Coupling times are given in Table I.

Periodically, 8 mg of deblocked peptide resin was dried and hydrolyzed with 1 ml of concentrated HCl and 1 ml of propionic acid for 2 hr at 130° in a sealed tube.[8] From preliminary results,

(1) The Salk Institute for Biological Studies, La Jolla, Calif.

(2) R. B. Merrifield, *Recent Progr. Horm. Res.*, **23**, 460 (1967).

(3) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis," Freeman, New York, N. Y., 1969.

(4) Private communication from Dr. Robert Colescott.

(5) Unpublished results of Professor A. B. Robinson while making portions of cytochrome c.

(6) This peptide was made for Dr. E. Eylar at The Salk Institute for Biological Studies, La Jolla Calif.

(7) Mercaptoethanol is unstable in trifluoroacetic acid and another reducing agent is more advisable. Unpublished observations of J. Sharp and F. Westall.

(8) Unpublished procedure of J. Scotchler and R. Losier.

TABLE I

Expt no.	Deblocking[a] agent	Coupling agent[b]	Coupling time, hr	Amino acids added[c] 1 O-Lys	2 Gly	3 Phe	4 Pro	5[d] Ser	6 Gln	7 Gly	8 Glu	9 Ala	10 Gly	11[e] Trp	12[d] Ser	13 Gly	14 Phe	15 Arg	16[d] Ser
1	HOAc–HCl	DCCI–CH_2Cl_2	6	1.44	1.01	0.98	1.00	0.90		0.34	0.49	0.35	0.32	0.30	0.36	0.31	0.40		0.35
	1% $HO(CH_2)_2SH$	Active esters–DMF	6						0.53										
		DCCI–DMF, CH_2Cl_2 (3:7 ml)	6															0.40	
2	Propionic–HCl	DCCI–CH_2Cl_2	6	1.20	1.05	1.00	1.00	0.93		0.35	0.60	0.39	0.36	0.30	0.41	0.35	0.46		0.39
	1% $HO(CH_2)_2SH$	Active esters–DMF	6						0.58										
		DCCI–DMF, CH_2Cl_2 (3:7 ml)	6															0.35	
3	TFA–CH_2Cl_2	DCCI–CH_2Cl_2	6	1.11	1.02	0.98	1.00	0.92											
	5% $HO(CH_2)_2SH$	Active esters–DMF							0.70										
4	TFA–CH_2Cl_2	DCCI–CH_2Cl_2	6	1.00	1.05	1.00	1.00	0.93		0.42	0.53	0.53	0.42						
	5% $HO(CH_2)_2SH$	Active ester–DMF, urea	24						0.98										
5	TFA–CH_2Cl_2	DCCI–CH_2Cl_2	6	1.00	1.02	0.96	1.00	1.00											
	5% $HO(CH_2)_2SH$	DCCI–DMF, CH_2Cl_2 (3:7 ml)	6							0.93	0.88	0.94	1.00	0.90	0.94	1.02	1.00		0.96
		Active ester–DMF, urea	24						0.97									0.98	
6	TFA–CH_2Cl_2	DCCI–CH_2Cl_2	6	1.01	1.01	0.98	1.00	1.00											
		Active ester–DMF, urea	24						0.98										
		DMF–DCCI coupling followed by CH_2Cl_2–DCCI coupling	6							0.80									
7	TFA–CH_2Cl_2	DCCI–CH_2Cl_2		1.00	0.98	1.00	0.98	0.96											
	5% $HO(CH_2)_2SH$	Active esters–DMF																	
		DCCI–DMF, CH_2Cl_2 (3:7 ml)																	
		Active ester–DMF, urea							0.97										
		CH_2Cl_2–DCCI coupling followed by DMF–DCCI coupling	6							0.81									

[a] Deblocking agents: HOAc saturated with HCl–propionic acid saturated with HCl–trifluoroacetic acid, methylene chloride, mercaptoethanol (40:55:5 by volume). [b] Coupling agents: 1.5 mmol DCCI per 10 ml of methylene chloride, 1.5 mmol of active ester dissolved in DMF with 1% acetic acid, 1.5 mmol DCCI dissolved in 3.0 ml of DMF (pH 7) and 7 ml of methylene chloride, 1.5 mmol of active ester dissolved in DMF with 1% acetic acid and 1.5 *M* in urea. [c] As determined by amino acid analysis of 2 hr propionic acid–HCl (1:1) hydrolysis. Values given in this table are based on total addition of proline as 1.00. Error ±5%. [d] Serine values are adjusted to take into account serine destruction upon hydrolysis. Approximately 20% of the serine was destroyed during hydrolysis. [e] Tryptophan values were determined spectrophotometrically by the procedure of Patcharnik: A. Patcharnik, W. B. Lawson, and B. Witkop, *J. Amer. Chem. Soc.*, 80, 4747 (1958).

it appears that all peptide bonds are routinely hydrolyzed. Amino acid analysis was performed with a Beckman amino acid analyzer which has an estimated accuracy of 5%.

Registry No.—DMF, 68-12-2; methylene chloride, 75-09-2.

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Synthesis of α,α-Dinitro-N′-fluorodiimide N-Oxides[1]

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Syntheses of N′-fluorodiimide N-oxides have been reported by reactions of tetrafluorohydrazine[2-6] or difluoramine[3,7] with nitroso compounds. Pseudonitroles gave α-nitro-N′-fluorodiimide N-oxides,[3,7] but α,α-dinitro-N′-fluorodiimide N-oxides have not been prepared directly; α,α-dinitro nitroso compounds are unknown.

$$R{-}NO + HNF_2 \longrightarrow R{-}\overset{\overset{O}{\uparrow}}{N}{=}NF + HF$$

$$R{-}NO + \cdot NF_2 \longrightarrow R{-}\overset{\overset{O}{\uparrow}}{N}{=}NF + [F\cdot]$$

In the present work, 1,1-dinitrobutyl-N′-fluorodiimide N-oxide was isolated from the reaction of the sodium salt of 1,1-dinitrobutane with tetrafluorohydrazine in methanol. The product was identified by analysis, and ir and nmr spectra. Most significantly, the ^{19}F signal, −125 ppm from trifluoroacetic acid, was in the region reported for other N′-fluorodiimide N-oxides. The mechanism for this reaction may involve 1,1-dinitro-1-nitrosobutane as a transient intermediate. The nitrosating agent may be nitrous acid resulting from the Neff reaction of the starting material; 1,1-dinitrobutane was also formed. An acid source is the abstraction of hydrogen from the solvent to give difluoramine which is readily dehydrofluorinated.

Preliminary work on this reaction was done with the salt of 1,1-dinitroethane, but the product was such a sensitive explosive that characterization could not be completed. The salt of nitroform did not react under these conditions. Sodium 2-propanenitronate on the other hand yielded only the coupling product, 2,3-dimethyl-2,3-dinitrobutane, as reported by Freeman.[8]

Experimental Section

Caution. Explosion shielding and remote manipulation are required for the N_2F_4 reaction and for product isolation.

1,1-Dinitrobutyl-N′-fluorodiimide N-Oxide.—A Fischer–Porter aerosol tube containing a solution of 14.8 g (0.10 mol) of 1,1-dinitrobutane and 0.10 mol of sodium methoxide in 45 ml of methanol was evacuated at liquid nitrogen temperature and filled with nitrogen several times. The tube was charged with 0.2 mol of tetrafluorohydrazine and the mixture was stirred for 20 hr at ambient temperature. The excess tetrafluorohydrazine was removed and most of the solvent was removed under vacuum. Methylene chloride (50 ml) was added and the solution was filtered and distilled to give 6.5 g of liquid, bp 46° (0.35 mm), which contained some 1,1-dinitrobutane. Chromatography with a 2 × 38 cm column of neutral active alumina and methylene chloride resulted in retention of the 1,1-dinitrobutane on the column as a bright yellow complex. Distillation of the eluent gave 1.3 g (6.2% yield) of 1,1-dinitro-1-butyl-N′-fluorodiimide N-oxide, bp 34–35° (0.15 mm).

Anal. Calcd for $C_4H_7N_4FO_5$: C, 22.86; H, 3.33; N, 26.7; F, 9.05. Found: C, 23.20; H, 3.17; N, 26.63; F, 9.0.

The proton nmr spectrum consisted of a triplet (J = 8 Hz) at δ 1.12 for CH_3, a multiplet at δ 1.9 for CH_3CH_2, and a triplet (J = 8 Hz) at δ 3.12 for the other methylene. The fluorine spectrum consisted of a broadened singlet at −125 ppm from external trifluoroacetic acid. The infrared spectrum consisted of bands at 3.42 (m), 3.53 (m), 6.4 (vs), 6.9 (m), 7.01 (m), 7.3 (m), 7.54 (s), 9.05 (w), 10.8 (w), 11.7 (m), 12.4 (m), and 13.2 μ (m).

Registry No.—1,1-Dinitrobutyl-N′-fluoridiimide N-oxide, 24903-89-7.

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Radical Anions Produced by Electrochemical Reduction of 1,3 Diketones[1]

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The half-life of radicals obtained by electrolysis of enolized 1,3 diketones is short because of rapid coupling reactions.[2] In DMSO as solvent, the reduction of the enolate anion of a 1,3 diketone causes decomposition *via* cleavage reactions.[2b] This latter fact appears to be inconsistent with one aspect of the pioneering work of Bauld and coworkers on the electron spin resonance (esr) spectra of dianion radicals.[3-6] These workers reported[6] esr data for the dianion radical formed by the electrochemical reduction of the dibenzoylmethide ion in DMF. On the basis of our observations of the electrochemical behavior of 1,3 diketones, we suggest that

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the spectrum obtained by Bauld and Brown[6] is actually that of the radical anion of 1-phenyl-1,2-propanedione rather than the dianion radical of dibenzoylmethane.

In Figure 1 the experimental spectrum (B) obtained from electrochemical reduction of dibenzoylmethide in DMF and the simulated spectrum (A) based on anticipated splitting constants for dibenzoylmethane dianion radical are reproduced from the original paper.[6] Also included is a simulated spectrum for the anion radical of 1-phenyl-1,2-propanedione using published splitting constants.[1,7,8] In spite of the relatively large line widths (*ca.* 0.2 gauss) the excellent agreement between the experimental spectrum (B) and the spectrum simulated for the 1-phenyl-1,2-propanedione radical anion (C) suggests that an unexpected reaction sequence is leading to the formation of the 1,2-diketone during electrochemical reduction of dibenzoylmethide.

In DMSO as solvent, several experiments demonstrate that the reduction of dibenzoylmethide is not a simple one electron process yielding the dianion radical. (1) Controlled potential coulometry at a potential cathodic of the half-wave potential of dibenzoylmethide ($E_{1/2}$ = −2.25 V *vs.* sce, 0.1 *M* tetra-*n*-butylammonium perchlorate in DMSO) resulted in a prolonged electrolysis with a total uptake of 3–4 electrons per dibenzoylmethide ion. (2) Cyclic voltammetric experiments indicated that the product of the reduction of dibenzoylmethide decomposed with a half-life of the order of 0.1 second. (3) Room temperature electrochemical reduction of dibenozylmethide in a cell in the esr spectrometer microwave cavity produced acetophenone radical anion. The observed splitting constants were identical with those reported for acetophenone radical anion in 1,2-dimethoxyethane.[9]

The mechanism by which acetophenone is produced is not known though either cleavage of the dianion radical itself or cleavage of the dibenzoylmethide catalyzed by bases generated during electrolysis seems likely. In any case, the production of acetophenone during the electrolysis provides a clue to the source of the 1-phenyl-1,2-propanedione radical anion detected by Bauld and Brown.[6]

In the original study[7] of the electrolytic reduction of acetophenone in DMF, an esr spectrum was obtained which proved to be inconsistent with the expected splitting constants for acetophenone radical anion. The species causing this spectrum was later identified[8] as the radical anion of 1-phenyl-1,2-propanedione. This unexpected product has only been observed when DMF is used as solvent. In DMSO or dimethoxyethane only the acetophenone radical anion is formed. It has been suggested[8] that in DMF the dianion of acetophenone may abstract a carbonyl group from the solvent. This is consistent with the observation[9] that the radical anion of 1-phenyl-1,2-propanedione is obtained only at potentials on the second polarographic wave of acetophenone in DMF.

We find that acetophenone radical anion is produced during reduction of dibenzoylmethide in DMF just as it is in DMSO. We suggest that under the conditions employed by Bauld and Brown[6] for the electrolysis of dibenzoylmethide in DMF, the acetophenone produced

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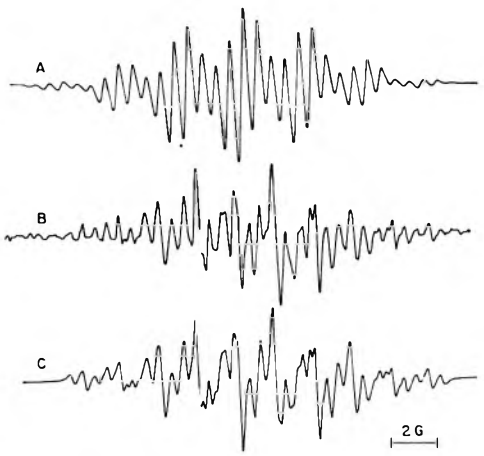

Figure 1.—A. Computer simulated esr spectrum for the dianion radical of dibenzoylmethide.[6] B. Experimental esr spectrum obtained by electrochemical reduction of dibenzoylmethide in DMF.[6] C. Computer simulated spectrum for the radical anion of 1-phenyl-1,2-propanedione.

by cleavage of dibenzoylmethide reacted further to produce 1-phenyl-1,2-propanedione radical anion which gave the spectrum in Figure 1B. This reassignment pertains only to the spectrum reported from electrochemical reduction of dibenzoylmethide in DMF. The partially resolved spectra obtained by chemical reduction in other solvents are probably due to the dianion radical as originally stated.[6]

Cleavage reactions are frequently encountered during the electrochemical reduction of 1,3-diketones. For example 2-*t*-butyl-1,3-diphenyl-1,3-propanedione is reduced ($E_{1/2}$ = −1.80 V *vs.* sce; controlled potential coulometric *n*-value = 1.1 equivalents/mol) to the radical anion of 3,3-dimethyl-1-phenyl-1-butanone (five nonequivalent ring protons with splitting constants of 6.40, 4.25, 3.54, 1.10 and 0.82 gauss; two equivalent methylene protons with splitting constant of 4.21 gauss). Other products of the cleavage reaction were not identified.

A 1,3-diketone giving a relatively stable radical anion is 2,2-dimethyl-1,3-diphenyl-1,3-propanedione. Its radical anion may be produced by controlled potential reduction ($E_{1/2}$ = −1.78 V *vs.* sce; *n*-value = 0.99 equivalents/mol). The spectrum was in agreement with the following assignment of splitting constants: six equivalent protons (*ortho* and *para*), 2.30 gauss; ten equivalent protons (*meta* and methyl), 0.50 gauss.

The radical slowly decomposes in DMSO yielding isobutyrophenone which may be identified in the electrolysis solution by polarography ($E_{1/2}$ = −2.03 V *vs.* sce) and by its esr spectrum obtained by further electrolysis of the above solution. The spectrum was identical with that obtained using authentic isobutyrophenone (splitting constant for α-proton: *ca.* 2.5 gauss. Very broad lines (0.4 gauss) are probably caused by unresolved methyl proton splittings).

The protons consumed in the formation of acetophenone during the electrolysis of dibenzoylmethide originate in the solvent. This was demonstrated by the acquisition of the esr spectrum of the radical anion of d_3-acetophenone during reduction of undeuterated dibenzoylmethide in d_3-DMSO. The splitting constant for the three methyl deuterons was 1.04 gauss and the ring proton splittings were unaffected by the deu-

terium substitution. No deuterium–hydrogen exchange was detectable by nmr in a solution of dibenzoylmethide and tetra-*n*-butylammonium perchlorate in d_6-DMSO indicating that no deuteration occurs prior to electrolysis.

Spectra may be obtained by electrolysis of dibenzoylmethane in THF at −60° or by electrolysis of dibenzoylmethane in DMSO containing 0.1 *M* tetra-*n*-butylammonium dibenzoylmethide at room temperature. These spectra are different than any so far reported for this system (benzil,[1] acetophenone, 1-phenyl-1,2-propanedione[6]) but unambiguous analyses of the spectra have not been attained. Definite assignment must await further studies now in progress.

Experimental Section

A Sargent Model XV polarograph with a Sargent IR compensator was used with a three electrode polarographic cell.[2a] The reference electrode was an aqueous saturated calomel electrode. The potentiostat for controlled potential coulometry was a Wenking Model 61 RS. The working electrode in the controlled potential electrolysis cell[2a] was a 30 cm² mercury pool. Cyclic voltammetric instrumentation was of conventional[10] design. The working electrode for cyclic voltammetry was a hanging mercury drop electrode (Model E410, Brinkmann Instruments) used in the polarographic cell mentioned above. The esr spectrometer was a Varian E-3. A Varian electrolytic cell was used for generation of radicals in the microwave cavity. The computer program for simulation of esr spectra was similar to that employed by Stone and Maki.[11]

Reagent grade DMSO was stirred over calcium hydride for at least 12 hr and distilled at reduced pressure just before use. Tetra-*n*-butylammonium perchlorate (Matheson) was used as received except for the cyclic voltammetric studies where it was recrystallized from ethyl acetate and vacuum dried. The dibenzoylmethide ion was prepared as its tetra-*n*-butylammonium salt.[2a] The 2-*t*-butyl-1,3-diphenyl-1,3-propanedione was prepared by a procedure analogous to the reported synthesis of 3-*t*-butyl-2,4-pentanedione:[12] mp 124.5–125°; nmr (CCl_4) δ 1.15 (s, 9, CH_3), 5.22 (s, 1, methine), 7.38 (m, 6, aromatic), 7.92 (m, 4, aromatic). *Anal.* Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.59; H, 7.23. The 2,2-dimethyl-1,3-diphenyl-1,3-propanedione was prepared as described previously:[13] mp 97.5–98° (99°);[13] nmr ($CDCl_3$) δ 1.67 (s, 6, CH_3), 7.33 (m, 6, aromatic), 7.85 (m, 4, aromatic).

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Production of Linear Acids or Esters by the Platinum–Tin-Catalyzed Carbonylation of α Olefins

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The carbonylation reaction of olefins in the presence of metal carbonyls or carbonyl precursors to form acids or esters was developed by Reppe and his coworkers.[1] For example, the reaction of ethylene with CO and water in the presence of nickel salts or nickel carbonyl yields propionic acid. When olefins larger than ethylene are reacted, the products consist of large amounts of branched isomers, in addition to the desired linear product, *i.e.*

$$RCH{=}CH_2 + CO + CH_3OH \longrightarrow RCH_2CH_2\overset{\overset{O}{\|}}{C}OCH_3 + RCH(CH_3)\overset{\overset{O}{\|}}{C}OCH_3$$

Furthermore, these reactions are generally carried out at temperatures above 150°, and a variety of other side reactions including polymerization, isomerization, and reduction can compete with the carbonylation.

Recent reports describe successful olefin carbonylation under relatively mild conditions which can avoid many of these competing reactions. Both palladium[2,3] and platinum[4] complexes were found to be catalytically active below 100°. However, none of these systems, as described, offers the combination of excellent yields and a high degree of product linearity. While systems for the formation of highly linear aldehydes[5,6] or alcohols[7] from α olefins are known, the purpose of this note is to describe a catalyst system that will effect rapid conversion of α olefins to highly linear acids or esters.

Jenner and Lindsey[4] found that a platinum salt–tin salt couple catalyzed the formation of esters from olefins at relatively low temperatures. However, their work was limited to olefins with less than six carbon atoms, and very high pressures (~800–1000 atm) with long reaction times (usually 10–16 hr) were necessitated. Additionally, propylene, the only straight chain, α monoolefin reported, gave a product mixture containing approximately equal amounts of methyl *n*-butyrate and methyl isobutyrate.

By utilizing a solvent such as acetone, methyl isobutyl ketone or 1,2-dimethoxyethane, and carefully controlling the reaction conditions, it has now been found that a H_2PtCl_6–$SnCl_2$ couple will catalyze carbonylation of olefins such as dodecene-1, in the presence of methanol, to highly linear (~85%) esters in 1 hr at 200 atm. The system has also been extended to acid synthesis under essentially the same conditions, by substituting water for the methanol. A typical reaction was carried out at 90° and 3000 psig of CO, with 1 mol % of H_2PtCl_6 and 5 mol % of $SnCl_2$ as catalyst, and acetone as solvent. Dodecene-1 conversion was 100% and product yield approximately 80% regardless of whether H_2O or methanol was utilized in the reaction. A small amount of olefin reduction occurred (2–4% of the olefin), but isomerization of the α olefin to internal olefins (mostly the 2-isomer) was the only major competing reaction. The acid (or ester) product was composed of approximately 85% of the straight chain isomer and 15% branched isomers. A mass spectral study showed that 80% of the branched product was the 2-methyl isomer.

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TABLE I

CARBONYLATION OF OLEFINS

Reaction	Olefin	Amt, mmol	H source	Time, hr	% conversion[a]	% yield[b]	% linearity
I	Propylene	250	CH_3OH	2	80	100	67
II	1-Hexene	250	CH_3OH	1	98	85	83
III	1-Hexene	250	H_2O	2	93	88	83
IV	1-Dodecene	268	CH_3OH	1	100	76	83
V	1-Dodecene	268	H_2O	2	100	74	86
VI	1-Tetradecene	268	CH_3OH	1	98	81	82
VII	Dodecenes[c]	268	H_2O	5	5	Mixture of products	
VIII	3-Heptene	250	CH_3OH	2	10	Mixture of products	
IX	2-Ethyl-1-hexene	250	CH_3OH	5	86	22	Compd 1[d]
						9	+ other alcohols
X	1,7-Octadiene	250	CH_3OH	2	100	64 diester	71
						35 mono-ester	66
XI	1-Dodecene + dodecenes[c]	268 268	CH_3OH	2	56	88	65

[a] Conversion (*via* vpc) = moles of olefin consumed/mole of olefin charged. [b] Yield (*via* vpc) = moles of product/mole of olefin consumed. [c] Randomized dodecenes, see Experimental Section. [d] Compound 1, $CH_3(CH_2)_3C(OH)(Et)CH_3$.

The results of the reaction of a number of olefins with acetone as a solvent are summarized in Table I. The reaction rates for ester formation tended to be faster than those for acid formation, and thus the shorter reaction times for the former. The carbonylation catalyzed by the platinum–tin catalyst appears to be general for hydrocarbon α olefins which contain hydrogen on the 2-carbon atom. Reactions I–VI demonstrate the high yields and excellent linearity that can be achieved with this system, propylene being the only α olefin that gave a product with linearity of less than 80%.

Internal olefins, however, were relatively inert to carbonylation under these conditions. Both 3-heptene and a mixture of randomized dodecenes gave very low conversions, and a mixture of products. The lower reactivity of the internal olefins suggested that it might be possible to react selectively α olefins from a mixture of isomers. Indeed, with a 50:50 mixture of 1-dodecene and random dodecene, approximately 50% of the olefin was carbonylated after 2 hours. However, the product linearity was less than expected. The attempted reaction of 2-ethyl-1-hexene was interesting, for when an ethyl group was substituted for the hydrogen on the 2-carbon of 1-hexene, olefin isomerization and hydration in typical Markovnikov fashion became the almost exclusive reaction. Protonation of the 1-carbon by chloroplatinic acid to give the tertiary carbonium ion is apparently much more rapid than carbonylation with this olefin.

The reaction with 1,7-octadiene indicates that the platinum–tin carbonylation system is applicable to terminal dienes, but the product distribution and linearity are complicated by the presence of the second double bond. The product mix was about 2:1 diester to unsaturated monoester. In both products the linearity dropped to near 70% from the 85% level found with monoolefins. A second problem was that the remaining double bond in the monoester was isomerized internally, indicating that any further carbonylation of the remaining olefin could yield only branched product.

The H_2PtCl_6–$SnCl_2$ couple has shown reactivity as a hydrogenation catalyst.[8,9] In the carbonylation work it offers the same advantage of ease of catalyst formation. Several other platinum compounds were found to catalyze carbonylation in the presence of $SnCl_2$, however only K_2PtCl_6 gave a rate of reaction comparable to H_2PtCl_6. The related palladium complex K_2PdCl_6 showed very little catalytic activity. Rather surprisingly, $(Ph_3P)_2PtCl_2$ gave only a trace of products with added $SnCl_2$. This is a catalyst that Bailar and Itatani used so successfully in selective olefin hydrogenation work.[10]

While the mechanism of the reaction is not completely understood, several comments are made here to aid in the understanding of this catalyst system. Neither H_2PtCl_6 nor $SnCl_2$ function individually. Previous work utilizing a H_2PtCl_6–$SnCl_2$ catalyst system for olefin hydrogenation has noted this same phenomenon.[8] Formation of a Pt–$SnCl_3$ complex apparently occurs. The $SnCl_3^-$ ligand, a strong π acceptor and a mild σ donor, modifies the platinum metal atom and enhances coordination of hydride or of olefin, thus triggering catalysis. The maximum rate of olefin carbonylation occurs for molar Sn:Pt ratios of 5 or greater. This is in contrast to Pietropaolo and coworkers[11] finding that the rate of ethylene absorption on $PtCl_4^{2-}$ promoted by $SnCl_3^-$ was highest for Sn:Pt ratios lower than 5. However, similar to our findings, Bailar and Itatani[10] noted higher reaction rates with Sn:Pt ratios higher than 5 in their olefin hydrogenation work.

It was found that water activates the K_2PtCl_6–$SnCl_2$ catalyst. In the ester syntheses this water requirement was usually satisfied by the water of hydration present on the $SnCl_2 \cdot 2H_2O$. Under completely anhydrous conditions however, no reaction occurred.

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For example, an attempted ester preparation using K_2PtCl_6 and anhydrous $SnCl_2$ with dimethoxyethane solvent gave no product, while the same reaction repeated with water added gave the desired carbonylation. Apparently a platinum hydride, which is a presumed intermediate in the catalysis, was formed by the interaction with water. This is another example of the formation of platinum hydrides from water, a reaction which has been noted previously.[12]

Experimental Section

Material.—$(Ph_3P)_2PtCl_2$ was prepared by the reported method.[13] Randomized dodecene was prepared by refluxing 1-dodecene with $PdCl_2$ for 16 hr. Vpc analysis of this random mixture showed 1-isomer = 2%, 2-isomer = 30%, 3-isomer = 24%, 4-isomer = 9%, other isomers = 34%. All other materials were best commercial grade used as purchased.

Typical Procedure for Acid Formation.—A 600 ml Magnedrive autoclave (Autoclave Engineers) was charged with 45 g (268 mmol) of 1-dodecene, 9 g (500 mmol) of water, 150 ml of acetone, 1.3 g (2.5 mmol) of $H_2PtCl_6 \cdot 6H_2O$, and 2.8 g (12.5 mmol) of $SnCl_2 \cdot 2H_2O$. The autoclave was sealed, flushed with carbon monoxide, and finally pressured to about 2000 psig with carbon monoxide. Stirring was begun and the autoclave was quickly heated to 90° and the pressure then adjusted to 3000 psi with more carbon monoxide. Reaction times were 1 or 2 hr depending on the rate of pressure drop.

Typical Procedure for Ester Formation.—This procedure was identical with that for acid synthesis, with 32 g (1 mol) of methanol substituted for water.

Analysis of Products.—The ester products were determined by vpc analysis of the recovered solutions. A Perkin-Elmer Model 9000 instrument was used. A 10 ft column packed with Carbowax 20M an Diatoport S was found to be suitable for analysis of the esters. A 150 ft capillary column coated with Carbowax 1540 gave a good separation of the isomerized olefins. Authentic samples of the linear products were available for use as standards. The individual products were trapped as they emerged from the chromatograph and were identified by mass spectrometric and nmr analysis. The acid products were esterified by BF_3–methanol reagent and analyzed as the methyl esters.

Catalysis by Other Platinum Group Catalysts.—The typical procedure for ester formation was repeated with several platinum compounds substituted for $H_2PtCl_3 \cdot 6H_2O$. A reaction utilizing 0.8 g (2.5 mmol) of $PtCl_4$ gave a 78% yield (100% conversion) of ester after 6 hr, 0.7 g (2.5 mmol) of $PtCl_2$ gave a 95% yield (30% conversion) after 6 hr, 1.2 g (2.5 mmol) of K_2PtCl_6 gave a 76% yield (100% conversion) after 1 hr, 2.0 g (2.5 mmol) of $(Ph_3P)_2PtCl_2$ gave a trace of ester after 6 hr, and 1 g (2.5 mmol) of K_2PdCl_6 gave a trace of ester after 2 hr.

Changing the Sn:Pt Ratio.—The typical procedure for acid formation when repeated using 1.7 g (7.5 mmol) of $SnCl_2 \cdot 2H_2O$ (Sn:Pt = 3) gave a 69% yield (35% conversion) of acid while 4.5 g (20 mmol) of $SnCl_2 \cdot 2H_2O$ (Sn:Pt = 8) gave a 70% yield (100% conversion) of acid.

Solvents Other Than Acetone.—The procedure for ester formation was repeated with three solvents, methyl isobutyl ketone, 1,2-dimethoxyethane, and tetrahydrofuran, substituted for acetone. No major difference in reactivity was noted.

Effect of Water on Catalytic Activity of K_2PtCl_6.—The procedure for ester formation was repeated utilizing 45 g (268 mmol) of dodecene-1, 32 g (1 mol) of methanol, 150 ml of 1,2-dimethoxy ethane, 1.2 g (2.5 mmol) of K_2PtCl_6, and 2.3 g (12.5 mmol) of anhydrous $SnCl_2$. Careful vpc analysis of the product mixture found no esters. This procedure was then repeated with 1.8 g (100 mmol) of water added. Vpc analysis indicated a 72% yield (32% conversion) of ester.

Registry No.—Propylene, 115-07-1; 1-hexene, 592-41-6; 1-dodecene, 112-41-4; 1-tetradecene, 1120-36-1; 2-ethyl-1-hexene, 1632-16-2; 1,7-octadiene, 3710-30-3.

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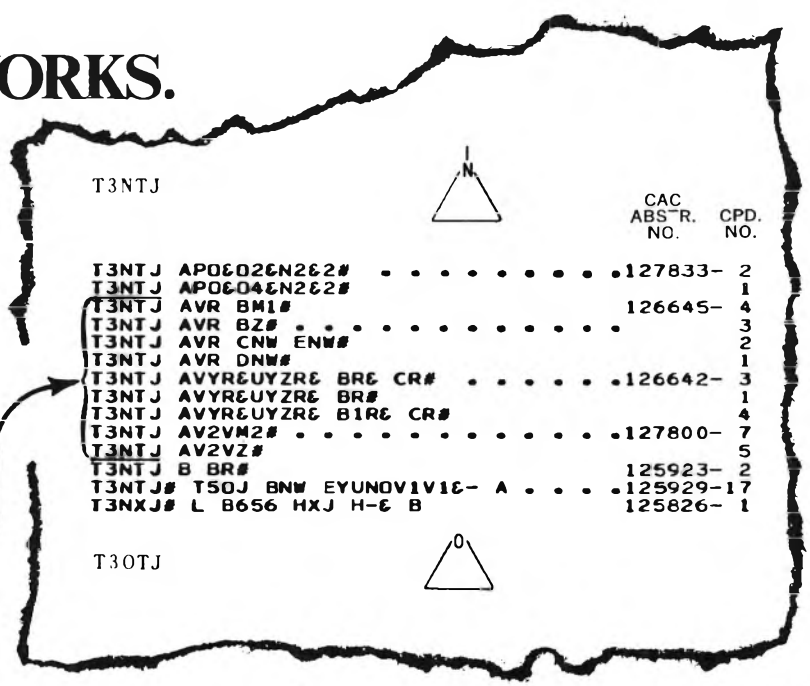

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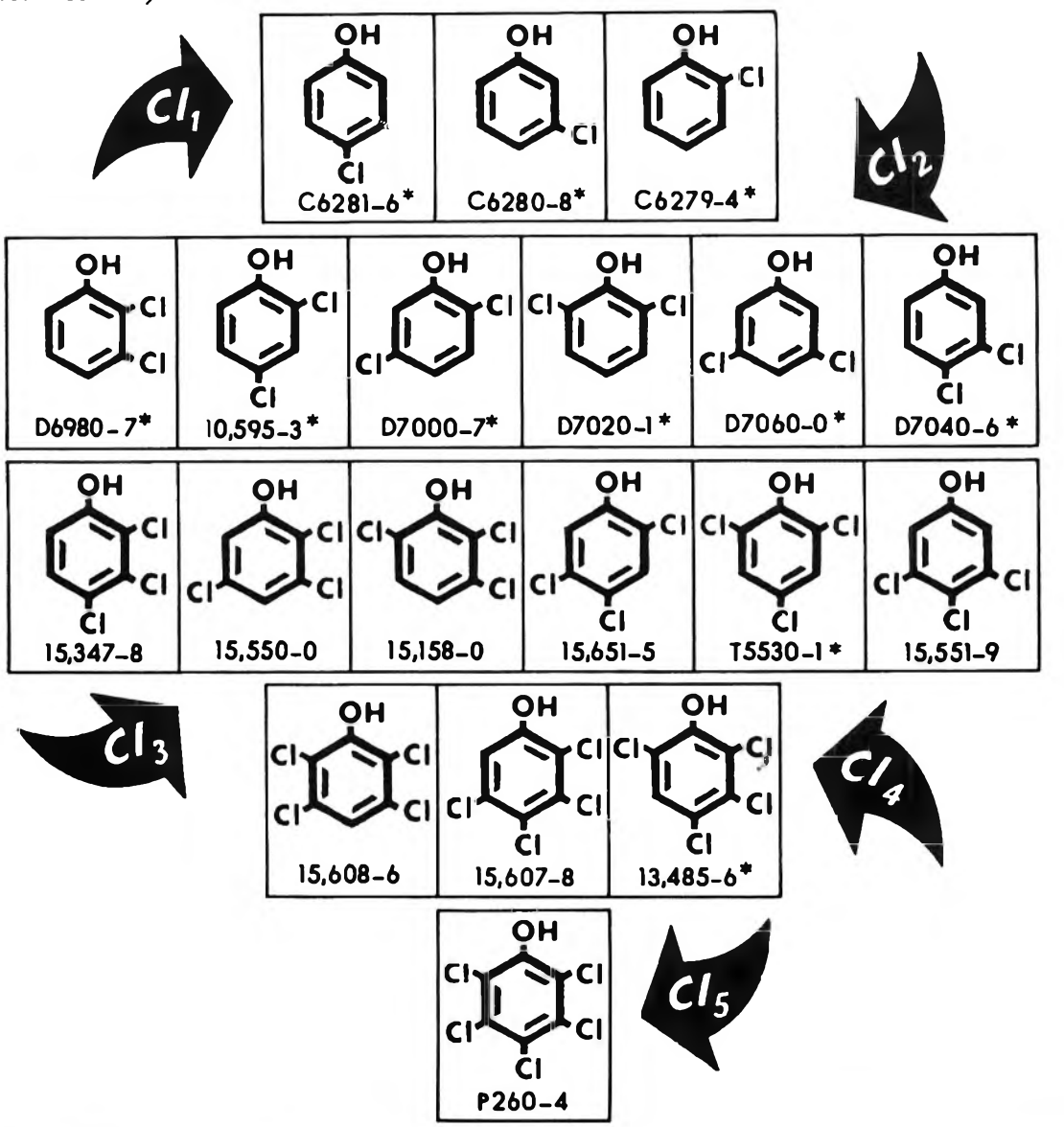

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